L Number	Hits	Search Text	DB	Time stamp
-	287	6-azamianserin mepirzapin mepirzepine mirtazapine mirtazepine mirtazipine (org adj "3770") promyrtil remergil remergon remeron zispin	USPAT; US-PGPUB	2003/06/04 17:30
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-	5929	headache	USPAT; US-PGPUB	2003/06/04 17:26
-	118	((6-azamianserin mepirzapin mepirzepine mirtazapine mirtazepine mirtazipine (org adj "3770") promyrtil remergil remergon remeron zispin) and (nsaid nsaids (non-steroid adj antiinflammatory) (non-steroidal adj (anti-inflammatory)) paracetamol acetaminophen tyleno aceclofenac antipyrine acetylsalicylic benoxaprofen butibufen caprofen celecoxib prioxicam lornoxicam ketorolac ibuprofen ibufenac ketoprofen meloxicam meclofenamic tenoxicam tolmetin tolfenamic numesulide (cox-2 adj inhibitor) (cox2 adj (inhibitor or antagonist)))) and headache	USPAT; US-PGPUB	2003/06/04 17:26
-	98	(((6-azamianserin mepirzapin mepirzepine mirtazapine mirtazepine mirtazipine (org adj "3770") promyrtil remergil remergon remeron zispin) and (nsaid nsaids (non-steroid adj antiinflammatory) (non-steroidal adj (anti-inflammatory)) paracetamol acetaminophen tyleno aceclofenac antipyrine acetylsalicylic benoxaprofen butibufen caprofen celecoxib prioxicam lornoxicam ketorolac ibuprofen ibufenac ketoprofen meloxicam meclofenamic tenoxicam tolmetin tolfenamic numesulide (cox-2 adj inhibitor) (cox2 adj (inhibitor or antagonist)))) and headache) and tension	USPAT; US-PGPUB	2003/06/04 17:26
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-	107	((6-azamianserin mepirzapin mepirzepine mirtazapine mirtazepine mirtazipine (org adj "3770") promyrtil remergil remergon remeron zispin)and headache) and tension	USPAT; US-PGPUB	2003/06/04 17:31

L1 ANSWER 1 OF 1 MEDLINE

ACCESSION NUMBER: **2001112752** MEDLINE

DOCUMENT NUMBER: 20580592 PubMed ID: 11139755

TITLE: [Treatment of tension headache].
Traitement des cephalees de tension.

AUTHOR: Schoenen J

CORPORATE SOURCE: Universite de Liege, Belgique.. schoenen.j@village.unnet.be

SOURCE: REVUE NEUROLOGIQUE, (2000) 156 Suppl 4 4S87-92. Ref: 31
Journal code: 2984779R. ISSN: 0035-3787.

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DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
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FILE SEGMENT: Priority Journals

ENTRY MONTH: 200102

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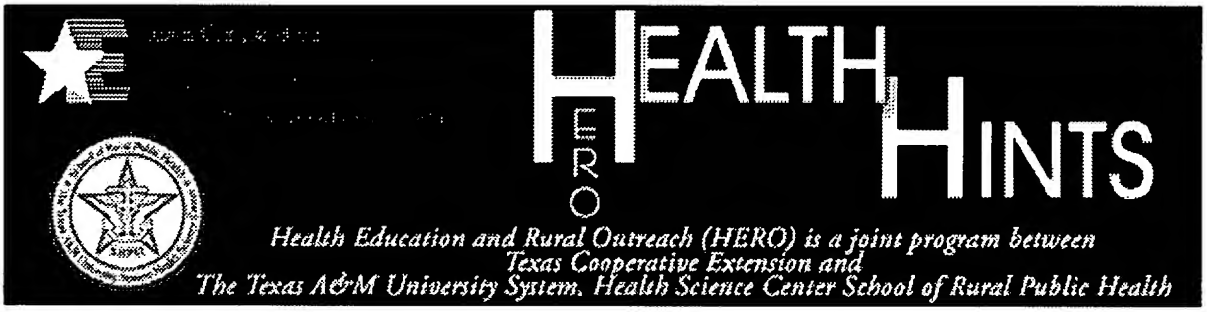
AB The scientific basis of tension- type headache suffers from the lack of precise pathophysiological knowledge and the heterogenecity of this disorder. Treatment of acute tension-type headache episodes is more effective with an NSAIDs (ibuprofen 400-800mg, naproxen 550-825mg, ketoprofen 50-75mg) than with aspirin or paracetamol. Caffein containing preparations of NSAIDs are slightly superior, but should not be taken frequently to avoid headache chronification. For chronic tension-type headache, relaxation therapies with EMG biofeedback and tricyclics have about the same efficacy rate of 40-50p.100. Physical therapy and acupuncture are in general less effective. There is thus clearly a need for better strategies, e.g. combination of available therapies and novel approaches.

=>



Volume 3, Number 10 - December, 1999

Headache

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Table of Contents

Headache

Oh my aching head...

Chronic headaches plague more than 45 million Americans (FDA, 1998; American Council for Headache Foundation, 1999). In a single year, nearly 90% of men and 95% of women experience at least one headache (American Council for Headache Foundation, 1996b). In this issue of HealthHints, we'll look at different types of headaches, why they occur, and how to best manage them. We'll also discuss how you and your doctor can identify your type of headache and headache triggers. Additionally, we'll discuss headache emergencies, when to contact your health care provider, and special headache concerns.

Primary or secondary

Headaches fall into two main categories -- primary and secondary.

1. A **primary** headache is an actual clinical condition and not a symptom of any other medical problem.

2. A **secondary** headache is caused by another medical condition, such as sinus disease, allergies, dental disorders, head injury, or brain tumors.

In this issue of HealthHints, we will focus mainly on primary headaches.

How headaches differ

Though there are about 12 types of headaches with more than 60 sub-types, there are three main varieties:

- Cluster headaches
- Migraine headaches
- Tension-type headaches (Farley, 1998)

A **cluster** headache is a particular type of headache that mainly affects men by a 6 to 1 ratio. It is characterized by intense but brief (30 minutes to 2 hours) pain in and around one eye occurring daily or several times per day in "clusters" that typically last for a couple of months. The sufferer then may go for many months with no headache. Along with the headache there are usually other incidents such as tearing and redness of the affected eye or stuffy nose.

A **migraine** headache is a particular kind of recurrent headache that often runs in families. To be considered a migraine, the headache must have four of the following characteristics:

- one-sided
- pulsating or throbbing
- pain is at least moderate if not severe

- pain is bad enough to interfere with or prevent normal activity
- pain is worsened by ordinary daily activities (e.g. stair climbing, housework)
- pain is accompanied by nausea
- sensitivity to light and noise comes with the pain.

There must be no other evidence of disease and a person must suffer 4 - 5 attacks before a doctor can be confident of the diagnosis.

A **tension-type headache** is just the opposite of a migraine **headache**. In a **tension**-type **headache**, the pain is:

- on both sides
- pressing and steady, rather than pulsating
- usually mild
- not incapacitating or worsened by daily activities
- not associated with nausea or sensitivity to light and noise.

(Definitions adapted from American Council for **Headache** Education, 1998a, and American Council for **Headache** Education, 1996c.)

What's causing my headache?

Both cluster and migraine headaches are considered vascular in nature. Vascular headaches involve dilation or swelling of the blood vessels in the tissue surrounding the head, which causes the pain (National **Headache** Foundation, 1999e).

On the other hand, a **tension**-type **headache** is not vascular. A **tension**-type **headache** is caused by the tightening of the muscles in the back of the neck and scalp.

Headache triggers

Although we know to some extent what physically happens to cause a **headache**, it is important to know what causes this physical reaction to begin with -- in other words, what triggers the **headache**.

There is still much to be learned about what triggers **cluster headaches**. Cluster headaches can be chronic -- occurring continually with no more than one week without a **headache**, or episodic -- occurring for a time, going away for a long, pain-free remission, and then recurring (American Medical Association, 1998b).

In either case, physical and environmental triggers that initiate cluster headaches have not been specifically identified. We do know, however, that substances that cause blood vessel swelling, such as alcohol, nitroglycerin, and histamine can accelerate an attack. Smoking can also increase the severity of the attack (National **Headache** Foundation, 1999). Keeping a **headache** diary may help as you and your health care provider try to investigate what

triggers your headaches.

Conversely, a multitude of physical and environmental triggers have been identified for **migraine headache** sufferers. These include the following:

- inconsistent sleep patterns
- hormones, such as changes during menstrual cycle, hormone replacement therapy, and birth control pills
- stress and anxiety
- weather changes
- glaring or fluorescent lights
- computer or TV screens
- strong odors - vapors or fumes
- high altitude
- diet, such as alcohol (particularly red wine), foods with MSG (monosodium glutamate), foods with tyramine (e.g., aged cheese), foods with nitrates and nitrites (e.g., preserved luncheon meats, bacon, or hot dogs), aspartame or artificial sweeteners, chocolate, caffeine-containing beverages, etc., or fasting or missing a meal (American Medical Association, 1998a; National **Headache** Foundation, 1999a; Wellness Councils of America, 1996).

Additionally, unlike cluster and **tension**-type headaches, migraine headaches have a hereditary influence in about 70-80% of sufferers (National **Headache** Foundation, 1999b).

Migraine sufferers differ in what triggers their headaches. Thus, keeping a **headache** diary and discussing it with your doctor can help you identify your individual migraine triggers.

Like cluster headaches there are two classifications of **tension-type headaches** -- episodic and chronic.

- **Episodic tension-type headaches** are usually triggered by some kind of environmental or internal stress. These stressors or triggers in turn stimulate an over-excitable state that lasts for the period of time the individual is under the stress. The **headache** may disappear with use of over-the-counter medications (analgesics), withdrawal from the source of stress, and a short period of relaxation (National **Headache** Foundation, 1999c).

- **Chronic tension-type headaches**, however, is a daily or continuous **headache**, which may vary in intensity during a 24-hour cycle, daily. There may also be some soreness, constricting band sensation, pressure-like sensation, or sensation of tight scalp. Some individuals may complain of early or frequent awakening from sleep, a sign of underlying depression (National **Headache** Foundation, 1999c). Triggers for chronic **tension**-type headaches may be more difficult to identify and require investigation through use of a **headache** diary shared with your health care provider.

Tracking your headaches

If you have recurring headaches, tracking your headaches with a **headache** diary can help you and your doctor to diagnose what types of headaches you are having, what is triggering them, and how best to manage them.

A **headache** diary is just a record of your **headache** symptoms. You should keep your diary for at least four episodes of **headache** to begin to see any type of pattern. Your diary should include the following elements:

- Date and time each **headache** started and stopped.
- Any factors that seem to trigger your **headache** (e.g., food, smoke, bright light, stress, activity).
- What you are doing when a **headache** strikes.
- Any foods you have eaten.
- The location and nature of the pain (e.g., throbbing, aching, stabbing, dull).
- The severity of the pain.
- Other physical symptoms, if any (e.g., nausea, vomiting, visual disturbances, sensitivity to light or noise).
- If you're a woman, note any association between headaches and your menstrual cycle, use of birth control pills, or hormone replacement therapy.

See the **Headache** Diary insert for place to keep your records.

(Adapted from Kemper, 1997; Wellness Councils of America, 1996.)

Headache emergencies: When to call your health care provider

You should call your doctor immediately if any of the following **headache** events occur:

- A very sudden, "thunderclap" **headache**.
- A sudden, severe **headache**, unlike you've ever had.
- **Headache** with stiff neck, fever, nausea, drowsiness, confusion.
- Sudden, severe **headache** with stiff neck developing soon after the **headache** starts.
- **Headache** with weakness, paralysis, numbness, visual disturbances, slurred speech, confusion, or behavior changes.
- **Headache** following a recent fall or blow to the head.

- Kemper, 1997

Headache prevention

Tracking your **headache** history through a **headache** diary is your first step toward prevention. Once you find out what events, foods, medications, or activities bring on a **headache**, you may be able to prevent or limit their recurrence by limiting or avoiding certain substances or activities (Kemper, 1997).

Here are some tips that may help prevent or limit your headaches:

- Reduce emotional stress. Take time to relax before and after events that cause a **headache**.
- Reduce physical stress. Change positions often and stretch every 30 minutes when doing desk work. Try to consciously relax your neck, jaw, shoulders and upper back.
- Exercise daily to reduce stress.
- Try massage as a way to reduce **tension**.
- Limit your caffeine intake to one to two cups per day. Cut down slowly to avoid caffeine-withdrawal headaches.
- Some women find that headaches improve if they discontinue their birth control. Consult your doctor about trying a non-hormonal form of birth control (Kemper, 1997).

Headache management

Despite efforts at preventing headaches, they may not be completely avoidable. Most **tension-type headaches** can be managed at home through the use of some of the following tips:

- When a **headache** starts, stop what you're doing and sit quietly for a moment. Close your eyes and try to relax your head and neck muscles. Inhale and exhale slowly.
- Take a break to stretch and relax. Gently and firmly massage your neck muscles.
- Apply heat with a heating pad, hot water bottle, or warm shower.
- Lie down in a dark room with a cool cloth on your forehead.
- Try aspirin, acetaminophen, or **ibuprofen** to help relieve your **headache**; however, be careful not to over use these over-the-counter products, which could result in a more severe **headache** (Kemper, 1997).

Although **vascular headaches** are often more severe than **tension**-type headaches, they can also be relieved through the use of some home care treatments:

- If possible, lie down in a darkened room. Place a cool cloth or ice pack on your forehead or temporal area and relax your body. **Note:** Ice packs that can be carried along with no refrigeration required are now available over the counter.
- Consciously relax your entire body starting with your eyes and forehead and working down to your toes.
- Try sleeping if you can.
- Try aspirin, acetaminophen, or **ibuprofen** to help relieve your **headache**. Remember, however, that using these medications too frequently can make your headaches more frequent or severe.
- If your doctor has prescribed **headache** medicine, take the recommended dose at first sign of an on-coming **headache** (Kemper, 1997).

Headache treatment

OTCs

When choosing medication to treat your headaches, the aisles and aisles of over-the-counter (OTC) pain relievers can be confusing. Are they all basically the same? Is one better for a specific type of **headache** than another?

The truth is, they are not all the same, and what works well for one person, may not work for another. Still, knowing the basics about OTC medications can help you to make a wise choice for your individual treatment.

There are four main groups of pain relievers:

- Aspirin products (e.g., Bayer, Bufferin)
- Acetaminophen products (e.g., Tylenol, Tylenol PM, Excedrin PM)
- NSAIDS, nonsteroidal anti-inflammatory drugs, such as **ibuprofen**, ketoprofen and naproxes sodium products (e.g., Advil, Aleve, Nuprin, Orudis KT)
- Combination products, which contain a combination of aspirin and caffeine or acetaminophen, aspirin, and caffeine (e.g., Anacin, Excedrin, Excedrin Aspirin Free, Excedrin for Migraine).

OCT medications with a combination including caffeine have shown to be more effective for some. Remember, however, that caffeine can also be the culprit of a **headache**. If you drink caffeine regularly, you may have caffeine withdrawal headaches at times. In this case, you may want to choose another option (Wellness Councils of America, 1996).

OTC medications are a good choice for milder migraines or **tension**-type headaches. If, however, the **headache** does not respond to these medications, taking multiple doses will not help and can hurt. Migraine and cluster **headache** sufferers may want to consult their doctors about acquiring a prescription dosage of these medications, which may be more effective in treating their headaches. The choice of pills, caplets, or tablets is mostly a consideration of what can be swallowed the easiest (American Council for **Headache** Education, 1996a).

Many people find OTC pain relievers convenient and effective. For those who have headaches that peak rapidly, however, the time the drug takes to work may render these options less attractive. Additionally, for those who have migraine with nausea or vomiting, it may interfere with the medication's effectiveness. Thus, other options may need consideration (American Council for **Headache** Education, 1998b).

Lozenges, sprays, suppositories, and injections

In addition to the four categories of oral OTCs, there are other medications that can be administered by prescription, which provide relief through different absorption routes in the body. These are primarily used in the treatment of vascular type headaches (e.g., migraine or cluster).

- **Sublingual tablets or lozenges** taken orally and held under the tongue are absorbed through the membrane lining of the mouth, and may act more quickly than

conventional tablets. (Conventional tablets like the OTCs mentioned earlier are absorbed through the gastrointestinal tract and must pass through the stomach and small intestine before entering the bloodstream.)

- **Nasal sprays or drops** (e.g., DHE or sumatriptan) may also be quicker to take effect than oral drugs because they are absorbed into the bloodstream through the membrane lining of the nose. Because they are easier to use than injected drugs, nasal sprays can be a good option for those who suffer nausea and vomiting with their headaches or have sever cluster or migraine headaches. The nasal products may take some practice, however, since correct positioning of the head during administration can effect efficiency.

- **Suppositories** are also effective for fast pain relief and a good choice for those with nausea and vomiting with their attacks. Suppositories are absorbed through the membrane of the rectum. Due to the development of nasal sprays, however, they are now less often used.

- **Self-injected drugs** generally provide the quickest relief because they are inserted straight into the bloodstream. There are several drawbacks, however, including inconvenience (as compared to oral or other medications), embarrassment of taking injections in public, and possibly more intense side effects. Injected drugs, however, may be the best option for someone who suffers rapid and severe **headache** attacks (American Council for **Headache** Foundation, What's the best medicine for my headaches, 1998b).

Special considerations: Children and headaches

Headaches are common in children, but are rarely a serious problem. Still, it can be difficult for parents or care providers to discern a **headache's** actual cause.

Here are some common causes of headaches among children. Asking questions about these areas can help you and your child discern the cause of the **headache**:

- Emotional **tension** is the most common cause of **headache** among children. This stress can be brought about by school, sports, relationships, or even the fun activities that can be overdone.
- Hunger is another cause. A daily breakfast and healthy after-school snack may help ward off headaches.
- Eyestrain can also produce headaches. Have your child's eyes checked regularly.
- Viral illnesses that cause fever, such as colds and flu may also result in **headache**.
- Imitation, although not an actual cause of **headache**, may be a reason for a child stating he has a **headache**. If you suffer a **headache**, try not to mention it too much, as children like to imitate their parents.

If your child has a **headache**, try talking with him. If the **headache** seems due to emotional stress, talking about the problem can help. Keep in mind, **tension**-type headaches among children are sometimes "attention" headaches. Quiet time and some extra attention may help

relieve the **headache** without pain relievers.

Here are some other home care tips to help your child when he suffers a **headache**:

- Play quietly with the child or read stories together.
- If the **headache** persists, have the child lay down in a darkened room with a cool cloth on his head.
- If non-drug treatments do not work, try acetaminophen at recommended doses for children. **Never give a child under 18 aspirin.** This could result in a disease known as Reye's Syndrome.

Call your health care provider:

- If the **headache** is severe and not relieved by relaxation or acetaminophen.
- If a severe **headache** occurs with signs of encephalitis or meningitis (i.e., inflammation of the brain, and inflammation of the tissue surrounding the brain and spinal cord, respectively) especially following a viral illness. These sign include:
  - severe **headache** with stiff neck, fever, nausea, and vomiting
  - drowsiness, lethargy, confusion, or delirium
  - bulging soft spot on the infant's head (when the baby is not crying).
- If the child's **headache** occurs 2-3 times a week or more.
- If you are using pain relievers more than once a week to control a child's **headache**.
- If you cannot discern a reasonable cause. (The child may share problems with someone other than a parent).
- If the headaches awaken the child at night or are worse early in the morning (Kemper, 1997).

Migraine with aura and stroke risk

Some people who suffer migraine headaches, also have what are known as auras accompanying their attacks. Auras are typically visual sensations of light, including light flashes, jagged lights, and distortion of images, shapes, sizes, and colors. Auras, however, may also include voices, numbness, or partial loss of vision.

Although visual disturbances can be related to local eye conditions, such as glaucoma, these disturbances may also be warning signs of a stroke, and are termed *transient ischemic attacks (TIA)* (National **Headache** Foundation, 1999f).

If a person in their 50s or 60s develops migraine-like symptoms for the first time, TIA is particularly suspect. (Migraines rarely start after age 40.) Headaches tend to occur in 25-39% of patients with this condition. Usually the carotid artery is diseased and the **headache** occurs on the same side as the affected carotid (National **Headache** Foundation, TIA, 1999d).

In addition to stroke risk among older adults, a study in the May, 1999 issue of *Neurology* suggests that 50% of people who have migraine headaches with aura also have a condition known as *patent foramen ovale*, a congenital opening between two chambers in the heart. *This opening is present in 1/3 of the general public, and is a known risk factor for the uncommon strokes that occur in young people* (American Association of Neurology, 1999).

To lower stroke risk, it is recommended that individuals who experience migraine with aura do the following:

- Establish an active relationship with a neurologist who can help you identify individual ways to lower your stroke risk.
- Do not smoke.
- For women sufferers, seek methods of birth control other than birth control pills (American Association of Neurology, 1999).

Educational Program Packet: "Headaches"

Don't forget about the educational program packet on headaches. This resource compliments and expands on the information in your *Healthwise Handbook* in a say-do format ready for your programming needs. Call Courtney Schoessow at 979-845-3850 for a copy.

Resource Extra

The Texas Department of Health has a new tool for community leaders and groups working to build healthier neighborhoods. The **"Road Map to a Healthier Neighborhood"** is a kit with information designed to help a community identify needs and resources, create a shared vision, design an action plan, and rally support for a community-based initiative.

This resource is available **free** at your request by calling 1-87-ROADMAP4 (1-877-623-6274)

Correction to January 1999 HealthHints Issue

Please make the following correction to the Body Mass Index (BMI) calculation in your January 1999 issue of HealthHints.

BMI should be calculated as follows

1. Weight X 700
2. Height X Height
3. Divide answer in #1 by answer in #2

Example:

1. 150 X 700 = 105,000
2. 67" x 67" = 4489
3. 105,000 divided by 4489 = 23.39

Sincerest apologies for any inconvenience this may have caused.

References:

American Association of Neurology (1999). Migraine with aura may signal increased stroke risk [on-line].
Available: http://www.aan.com/public/**headache**/Wmigraine.htm.

American Council for **Headache** Education (1998a). Glossary of **headache** terms [on-line].
Available:
http://www.achenet.org/resources/glossary.php.

American Council for **Headache** Education (1999). **Headache** facts: What everyone should know [on-line].
Available: http://www.achenet.org/resources/headfact.php.

American Council for **Headache** Education (1996a). OTCs and occasional **headache** [on-line]. Available:
http://www.achenet.org/otcsand.htm.

American Council for **Headache** Education (1996b). Understanding **headache** [on-line].
Available:
http://www.achenet.org/prevention/understanding/.

American Council for **Headache** Education (1996c). What causes **headache**? [on-line].
Available:
http://www.achenet.org/understanding/causes.php.

American Council for Headache Education (1998b). What's the best medicine for my headaches? [on-line].
Available: http://www.achenet.org/resources/bestmed.php.

American Medical Association (1998a). Migraine: How is migraine treated [on-line].
Available:
http://www.ama-assn.org/insight/spec_con/migraine/howis.html.

American Medical Association (1998b). Migraine: Other headache types and their treatment [on-line].
Available: http://www.ama-assn.org/insight/spec_con/migraine/other.html.

Farley, D. (1992). Migraine, cluster, and tension: Headache misery may yield to proper treatment [on-line].
Available: http://www.fda.gov/bbs/topics/CONSUMER/CON00168.html.

Kemper, D.W. (1997). *Healthwise Handbook*, 13th ed. Healthwise, Incorporated: Boise, Idaho, pp 143, 167-153.

National Headache Foundation (1999). Cluster headaches [on-line]. Available:
http://www.headaches.org/topicsheets/clusterheadache.html.

National Headache Foundation (1999a). Environmental and physical factors [on-line].
Available:
http://www.headaches.org/topicsheets/envir_physical.html.

National Headache Foundation (1999b). Migraine [on-line]. Available:
http://www.headaches.org/topicsheets/migraine.html.

National Headache Foundation (1999c). Tension-type headache [one-line]. Available:
http://www.headaches.org/topicsheets/tension_type.html.

National Headache Foundation (1999d). Transient ischemic attacks [on-line]. Available:
http://www.headaches.org/topicsheets/tia.html.

National Headache Foundation (1999e). Vascular headaches [on-line]. Available:
http://www.headaches.org/topicsheets/vascular.html.

National Headache Foundation (1999f). Visual disturbances [on-line]. Available:
http://www.headaches.org/topicsheets/visualdisturbances.html.

Wellness Councils of American and Excedrin Headache Resource Center (1996). *Headache: What You Should Know, What You Can Do*. Bristol-Myers Squibb.

Websites with reliable information

- Cluster **Headache** (NHF)
  [http://www.headaches.org/consumer/topicsheets/clusterheadache.html]
- **Headache** (Mayo Clinic)
  [http://www.mayoclinic.com/findinformation/conditioncenters/invoke.cfm?objectid=94CDF0
- **Headache** Facts: What Everyone Should Know (ACHE)
  [http://www.achenet.org/resources/headfact.php]
- Migraine (NHF)
  [http://www.headaches.org/consumer/topicsheets/migraine.html]
- Oooh, Your Aching Head! (KidsHealth)
  [http://www.kidshealth.org/kid/ill_injure/sick/**headache**.html]
- OTCs and Occasional **Headache** (ACHE)
  [http://www.achenet.org/prevention/understanding/relief.php]
- **Tension**-type **Headache** (NHF)
  [http://www.headaches.org/consumer/topicsheets/tension_type.html]
- Understanding **Headache** (ACHE)
  [http://www.achenet.org/prevention/understanding/]
- What Causes **Headache**? (ACHE)
  http://www.achenet.org/understanding/causes.php]

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HEADACHE

THE JOURNAL OF HEAD AND FACE PAIN

OCTOBER, 1998

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ABSTRACTS

MIGRAINE

Sumatriptan injection reduces productivity loss during a migraine attack: Results of a double-blind, placebo-controlled trial

Cady RC, Ryan R, Jhingran P, OQuinn S, Pait DG.

Objective: To evaluate the impact of sumatriptan succinate injection compared with placebo on productivity loss during a migraine attack in the workplace.

Design: Randomized, double-blind, placebo-controlled, parallel-group clinical trial.

Setting: Fifteen clinical centers in the United States.

Patients: One hundred thirty-five patients 18 years and older diagnosed as having migraine according to International Headache Society criteria.

Interventions: Patients self-administered sumatriptan injection (6 mg) or matching placebo to treat a moderate or severe migraine occurring within the first 4 hours of a minimum 8-hour work shift.

Main Outcome Measures: Mean productivity loss 2 hours after dosing and across the work shift; percentages of patients returning to normal work performance within 2 hours after dosing and across the work shift; percentages of patients experiencing headache relief (reduction of moderate or severe predose pain to mild or no pain) 1 and 2 hours after dosing.

Results: Mean productivity loss was significantly (P less than or equal to.002) lower in the sumatriptan group compared with the placebo group both during the 2-hour postdose period (sumatriptan, 39 minutes; placebo, 54 minutes) and across the work shift (sumatriptan, 86 minutes; placebo, 168 minutes). Significantly (P<.001) greater percentages of patients in the

sumatriptan group compared with the placebo group returned to normal work performance by 2 hours after dosing (sumatriptan, 52%; placebo, 9%) and across the work shift (sumatriptan, 66%; placebo, 18%). Significantly (P less than or equal to.001) greater percentages of patients in the sumatriptan group compared with the placebo group experienced headache relief 1 hour after dosing (sumatriptan, 69%; placebo, 18%) and 2 hours after dosing (sumatriptan, 79%; placebo, 32%).

Conclusion: Sumatriptan reduced migraine-associated productivity loss during a minimum 8-hour work shift by approximately 50% compared with placebo and alleviated headache in more than three fourths of patients.

Comment: No real surprise that sumatriptan is 50% more effective than placebo in the workplace. However, this is an important study for those developing evidence-based guidelines. When less expensive therapies are ineffective or likely to be ineffective (e.g., severe headache with early and severe GI symtpoms and peak intensity reached in 1 or less), the injectable sumatriptan and intranasal dihydroergotamine are cost-effective.

(*Arch Intern Med* 1998 11;158(9):1013-1018)

Tolfenamic acid rapid release versus sumatriptan in the acute treatment of migraine: Comparable effect in a double-blind, randomized, controlled, parallel-group study

Myllyla VV, Havanka H, Herrala L, Kangasniemi P, Rautakorpi I, Turkka J, Vapaatalo H, Eskerod O.

The efficacy and safety of tolfenamic acid and oral sumatriptan in the acute treatment of migraine was studied at five neurological centers in Finland. One hundred forty-one patients experiencing 289 migraine attacks, fulfilling the diagnostic criteria for migraine with or without aura as defined by the International Headache Society, were randomized. For first attacks, 77% of patients receiving tolfenamic acid experienced a reduction of the initial severe or moderate headache to mild or no headache after 2 hours, as compared to 79% in the sumatriptan group and 29% in the placebo group. No significant difference was found between active treatments (P=0.85. 95% CI [-22%, 18%]), however, both active treatments were significantly better than placebo; P=0.001, 95% CI (26%, 69%) for tolfenamic acid and P=0.001, 95% CI (28%, 71%) for sumatriptan. For second attacks, results were similar with 70% of patients receiving tolfenamic acid experiencing relief, as compared to 64% in the sumatriptan group and 39% in the placebo group. No significant differences were observed in accompanying symptoms. Both drugs were well tolerated with the frequency of adverse events: 30% for tolfenamic acid and 41% for sumatriptan, a nonsignificant difference. In this study, tolfenamic acid and oral sumatriptan are comparably effective in the acute treatment of migraine. When comparably effective, factors like individual effect, tolerance, and cost of treatment should be considered when prescribing migraine medication.

Comment: Cost matters. Patients who respond well to a nonsteroidal anti-inflammatory agent should use these as first-line therapy. However, physicians and patients should have access to other agents when they fail.

(*Headache* 1998;38(3):201-207)

Migraine: Diagnosis and rational treatment

Winner PK.

When patients present with severe, incapacitating headaches, they are often concerned with whether or not they are suffering from a severe illness, or even a brain tumor. The next concern is the relief of the incapacitating pain. In adults, primary headache disorders account for approximately 80% of the headaches experienced, compared with 20% for secondary headache disorders. Migraine, one of the most common disabling headaches, afflicts more than 18 million women and 5 million men with severe, incapacitating pain. Determining which headache patient requires a detailed evaluation can be facilitated by the use of the International Headache Society criteria, a thorough history, and a complete physical examination. The management of headaches, specifically migraines, encompasses both pharmacologic and nonpharmacologic strategies, requiring the integration of new medications into our established treatment profiles. Selecting appropriate pharmacologic therapy also requires the recognition of comorbid conditions associated with headache. Physicians and allied health care professionals can improve the quality of life and headache patients by instituting and coordinating comprehensive therapeutic approaches.

Comment: The figure of 20% for secondary headache seems high, especially if one is considering periodic nonprogressive headaches.

(*Int J Fertil Womens Med* 1998;43(2):104-110)

MSQ: Migraine-Specific Quality-of-Life Questionnaire -Further investigation of the factor structure

Jhingran P, Davis SM, LaVange LM, Miller DW, Helms RW.

MSQ, the 16-item Migraine-Specific Quality-of-Life Questionnaire (Version 1.0), was developed by GlaxoWellcome Inc. to assess the effect of migraine and its treatment on patients' health-related quality of life (HR-QOL). The MSQ was hypothesised to measure 3 meaningful dimensions: (i) Role Function-Restrictive; (ii) Role Function-Preventive; and (iii) Emotional Function. The objective of this research was to further investigate the number of dimensions as well as the items contained in each dimension through principal components factor analysis of clinical trial data. Secondary objectives were to determine whether the factor structure changed in post-treatment visits compared with screening visits, to make recommendations for coding the MSQ when the patient did not have a migraine in the previous 4 weeks, and to modify the MSQ if so indicated by this research. Results supported the existence of 3 distinct factors which agreed strongly with the hypothesised dimensions. The analysis of post-treatment data suggested that the underlying factor structure of the MSQ varies as a result of treatment. Based on evaluations of the 'did not have a migraine' response, it was concluded that it be dropped from the MSQ. All these changes have been incorporated into MSQ (Version 2.0) which is being evaluated in studies to determine if its psychometric properties are different than the properties of the previous version.

Comment: After 20 years and more than 7000 patients, I have the impression that preventive therapy must reduce the number of attacks by at least 50% to provide "meaningful" relief. Abortive therapies that provide complete relief of symptoms within 2 hours are also generally considered "effective" by patients.

(*Pharmacoeconomics* 1998;13(6):707-717)

Sumatriptan: An updated review of its use in migraine

Perry CM, Markham A.

Sumatriptan is a selective agonist at serotonin 5-HT1-like receptors, including 5-HT1B/1D subtypes. It is an effective treatment for acute migraine attacks and the injectable form has also shown efficacy in the treatment of cluster headaches. In placebo-controlled clinical trials, sumatriptan, administered subcutaneously, orally, intranasally or rectally was significantly more effective than placebo in relieving migraine headache and in producing resolution or reduction of other symptoms associated with migraine, including nausea, photophobia and phonophobia. Improvements in clinical disability were also significantly greater after sumatriptan than after placebo. Headache recurred in 21 to 57% of patients who received oral or subcutaneous sumatriptan, but most patients responded to a second dose of the drug. Results of comparative trials showed that subcutaneous sumatriptan 6mg was significantly more effective than either patients' usual antimigraine treatments or intranasal dihydroergotamine mesylate 1mg in relieving migraine headache. Subcutaneous sumatriptan 6mg and subcutaneous dihydroergotamine mesylate 1mg provided similarly effective migraine relief, but the headache recurrence rate was significantly higher after sumatriptan than after this formulation of dihydroergotamine mesylate. Response rates achieved after oral sumatriptan were similar to those reported after treatment with oral naratriptan, rizatriptan or lysine acetylsalicylate plus metoclopramide. Treatment of acute migraine attacks with oral or subcutaneous sumatriptan leads to less loss of workplace productivity than other antimigraine therapies. Several pharmacoeconomic analyses showed that gains in workplace productivity in sumatriptan recipients ranged from 12.1 to 89.8 hours per patient per year. Significant improvements from baseline in overall health-related quality-of-life scores were also experienced by sumatriptan recipients. Sumatriptan is generally well tolerated. Nausea, vomiting, malaise and fatigue are the most common adverse events with oral sumatriptan. Injection site reactions occur in 10 to 40% of patients receiving the drug subcutaneously. A bitter taste at the back of the mouth occurs frequently after intranasal administration. Serious adverse events occur in about 0.14% of patients with migraine treated with sumatriptan. As the drug is associated with the rare development of cardiovascular effects, it is contraindicated in patients with a history of cardiovascular disease.

Conclusions: Despite its relatively high acquisition cost, reductions in lost workplace productivity experienced by patients treated with sumatriptan may result in savings in the overall cost of migraine to society. Thus, sumatriptan is a useful first-or second-line treatment option for patients with moderate or severe migraine.

(*Drugs* 1998;55(6):889-922)

Magnesium for migraine: Rationale for use and therapeutic potential

Mauskop A, Altura BM.

Magnesium deficiency can be assessed using serum ionized magnesium level, which appears to be a much more sensitive indicator of magnesium status than total serum or intracellular levels of this ion. In vitro and in vivo studies indicate that magnesium deficiency could play a contributing role in the pathogenesis of migraine in up to 50% of patients. In support of these findings, results from a single study indicate that intravenous infusion of magnesium sulfate can produce prompt and sustained relief of a migraine attack in half of patients. In this study, 85% of responders had low serum ionised magnesium levels, while 85% of non-responders had normal levels. Prophylactic oral magnesium supplementation has been shown to be effective in 2 double-blind trials. But ineffective in another. A possible reason for the lack of response reported in the latter study could be poor absorption of magnesium from the preparation used. Chelated magnesium diglycinate appears to be one of the better absorbed preparations. Despite the absence of definitive large scale studies, we recommend magnesium supplementation (chelated magnesium diglycinate 600 mg/day) in patients who experience migraine. This recommendation is based on the excellent safety profile and low cost of the supplementation, and the large amount of experimental and clinical data that support the use of this therapy.

Comment: Magnesium is a coenzyme for membrane-bound adenosine triphosphatase (ATPase) and is essential to the activity of a large number of other vital enzymes. Magnesium metabolism is closely linked to that of potassium, and magnesium deficiency may be a cause of hypokalemia unresponsive to potassium replacement. Also, magnesium acts as a calcium antagonist and vasodilator. In addition to its possible benefit for migraine, magnesium supplementation, 300-500 mg daily, has improved premenstrual syndrome (PMS) symptoms of mood changes, fluid retention, and food cravings, although the existence of magnesium deficiency in patients with PMS is currently controversial. The most common cause of magnesium deficiency is diuresis. Conditions which increase the requirements for magnesium are chronic alcoholism, diabetic ketoacidosis, gastrointestinal disease (chronic diarrhea, Crohn's, ulcerative colitis), hyperaldosteronism, hypercalcemia, hypomagnesemic hypocalcemia, hypomagnesemic hypokalemia, hyperparathyroidism, hyperthyroidism, pancreatic insufficiency, renal tubular acidosis, stress, and patients receiving thiazide or loop diuretics, cisplatin, amphotericin B therapy, cyclosporine, gentamicin, or digitalis glycosides, or are on total parenteral nutrition (TPN) therapy. Physicians may first suspect hypomagnesemia when chemistry profiles show hypocalcemia or hypokalemia. Neurologic abnormalities include lethargy, confusion, tremor, fasciculations, ataxia, nystagmus, tetany, and seizures. ECG abnormalities include prolonged PR and QT intervals. Magnesium deficiency may also cause symptoms of cardiac insufficiency, potentiation of digitalis toxicity, cardiac arrhythmias (including ventricular tachycardia, ventricular fibrillation, and torsades de pointes), and sudden death. Headache is not a symptom of magnesium deficiency. If one could show that lowering serum magnesium in the "responders" described above precipitates a typical migraine attack, the importance of magnesium deficiency in migraine would be easier to accept. Symptoms of hypermagnesemia include anorexia, nausea, vomiting, lethargy, muscular weakness, hyporeflexia, and hypotension. Marked hypermagnesemia may produce coma, seizures, respiratory depression, or cardiac arrest. Patients at greatest risk for magnesium toxicity include those with heart block, myocardial damage, or severe renal impairment.

(*CNS Drugs* 1998;9(3):185-190)

Familial hemiplegic migraine with irreversible brain damage

Hayashi R, Tachikawa H, Watanabe R, Honda M, Katsumata Y.

Familial hemiplegic migraine (FHM) is an autosomal dominant syndrome characterized by recurrent episodes of varying degrees of hemiparesis associated with migraine. The aura including hemiparesis may be prolonged and in severe attacks may often be associated with confusion or coma. We describe a case of FHM whose aura was atypically prolonged and resulted in irreversible brain deficit which on magnetic resonance imaging (MRI) was suggestive of cortical hyperperfusion. A subsequent MRI showed left brain atrophy.

(*Internal Med* 1998;37(2):166-168)

A pharmacokinetic interaction study of avitriptan and propranolol

Marathe PH, Greene DS, Kollia GD, Barbhaiya RH.

Objective: To assess whether a clinically significant change in the pharmacokinetics of avitriptan and propranolol is observed in healthy subjects after coadministration of the two drugs.

Methods: The pharmacokinetics of avitriptan and propranolol were investigated when the two drugs administered separately and when two 150 mg doses of avitriptan 2 hours apart were added to a steady-state regimen (80 mg twice a day) of propranolol. The pharmacokinetics of metabolites of avitriptan (N-desmethylavitriptan, methoxypyrimidinyl piperazine, and O-desmethylavitriptan) and the pharmacokinetics of 4-hydroxypropranolol were also assessed.

Results: Administration of avitriptan alone and together with propranolol resulted in small increases in mean blood pressure and small decreases in heart rate. Administration of propranolol resulted in lowering of blood pressure and heart rate consistent with the beta-blocking actions of propranolol. There were no changes in the pharmacokinetics of avitriptan after coadministration with propranolol. However, area under the plasma concentration-time curve (AUC) of propranolol showed a 20% increase after coadministration with avitriptan, whereas the AUC of 4-hydroxypropranolol significantly decreased. Avitriptan therefore appeared to affect the metabolism of propranolol to 4-hydroxy-propranolol. The peak plasma concentration and AUC for N-desmethylavitriptan and the AUC for methoxypyrimidinyl piperazine also showed statistically significant increases (about 25%) when avitriptan was coadministered with propranolol.

Conclusions: Considering the wide safety margin of propranolol, the increase in the exposure is not clinically significant. The increase in the exposure to the metabolites of avitriptan is also not considered to be clinically significant because the metabolite contribution to the pharmacologic activity or side effects is expected to be minimal. Based on these findings, avitriptan may be added to a steady-state regimen of propranolol as an abortive antimigraine

therapy.

Comment: Propranolol therapy may have no clinically significant effect with avitriptan but may be a significant factor for rizatriptan. In a study of concurrent administration of propranolol 240 mg/day and a single dose of rizatriptan 10 mg in healthy subjects (n=11), mean plasma AUC for rizatriptan was increased by 70% during propranolol administration, and a four-fold increase was observed in one subject.

(*Clin Pharmacol Ther* 1998;63(3):367-378)

The pharmacodynamics and pharmacokinetics of the 5HT(1B/1D)-agonist zolmitriptan in healthy young and elderly men and women

Peck RW, Seaber EJ, Dixon RM, Layton GR, Weatherley BC, Jackson SHD, Rolan PE, Posner J.

Objective: Zolmitriptan is a selective 5HT(1B/1D)-agonist for the treatment of migraine. In this study we investigated the cardiovascular and central nervous system effects and the pharmacokinetics of zolmitriptan in young and elderly adults.

Methods: Twelve young adult and 12 elderly volunteers received single doses of 5, 10, and 15 mg zolmitriptan during a randomizd, double-blind, placebo-controlled study. Blood pressure, heart rate, ECG, and central nervous system effects were monitored, and pharmacokinetic parameters of zolmitriptan and its metabolites calculated.

Results: Zolmitriptan did not affect heart rate. Mean systolic BP was 16 mm Hg higher after zolmitriptan than after placebo. Mean peak diastolic pressure was 6 to 10 mm Hg higher in both age groups. These changes were transient. Postural changes in blood pressure were unaffected. There was a dose-related increase in sedation, but the magnitude of the effects was small. Mean observed peak plasma concentration (C-max) and area under the plasma concentration-time profile [AUC-(0-infinity)] for zolmitriptan and its active N-desmethyl metabolite were similar in both age groups but higher in young women than in young men. Metabolite/parent ratios were higher in young men. No such differences were apparent in the elderly. The gender-related difference is probably the result of greater first-pass metabolism in young men. Zolmitriptan half-life was 2.8 to 3.6 hours in the elderly compared with 2.7 to 2.9 hours in young adults. Mean C-max and AUC(0-infinity) for the inactive, N-oxide, and the indole acetic acid metabolites were higher in the elderly, associated with lower renal clearance.

Conclusions: Zolmitriptan was well tolerated, with an effect of age on its effects on blood pressure and the pharmacokinetics of its metabolites. The data suggest no need for dose adjustment for age. In young subjects, concentrations were higher in women than in men, but the difference were insufficient to justify dosage adjustment.

Comment: Could a reduction in dosage reduce side effects for a 100 pound woman? Could an increase in dosage increase efficacy in a 225 pound man? Maybe one size fits all. Maybe not.

(*Clin Pharmacol Ther* 1998;63(3):342-353)

Efficacy and safety of sumatriptan tablets (25 mg, 50 mg, and 100 mg) in the acute treatment of migraine: Defining the optimum doses of oral sumatriptan

Pfaffenrath V, Cunin G, Sjonell G, Prendergast S.

That sumatriptan tablets are effective and well tolerated in the acute treatment of migraine has been established, but the relationship between dose and efficacy has not been adequately defined to date in clinical trials. This multinational double-blind trial (N=1003) in which patients treated up to three migraine attacks with sumatriptan 25 mg, 50 mg, 100 mg, or placebo, with a second independently randomized dose for headache recurrence, evaluated the efficacy and tolerability of three doses of sumatriptan. The results demonstrate that all doses of sumatriptan were superior ($P<0.05$) to placebo in reducing moderate or severe predose headache to mild or no headache 4 hours postdose for each of the three treated attacks; sumatriptan 50 mg and 100 mg were each superior ($P<0.05$) to sumatriptan 25 mg 4 hours postdose for two of three attacks. Sumatriptan (all doses) was similarly effective at relieving nausea and photophobia or phonophobia or both and at reducing clinical disability. Headache recurrence was experienced by similar proportions of patients across treatment groups (35% to 48% after placebo; 26% to 39% after sumatriptan). Relief of recurrent headache 2 hours after the second dose of study medication occurred in greater percentages of patients using any dose of sumatriptan compared with patients using placebo to treat recurrence. The incidence of adverse events with 25-mg and 50-mg sumatriptan tablets was similar to the incidence with placebo and lower than the incidence with 100-mg sumatriptan tablets. These data provide the first demonstration from a large well-controlled clinical trial that both the 50-and 100-mg doses are more effective than the 25-mg dose and that the 50-mg dose is associated with a lower incidence of adverse events than the 100-mg dose.

(*Headache* 1998;38(3):184-190)

Features of Leao's spreading depression in patients with lesions near sensory cortex

Loeb JA.

Although it has been produced experimentally only in animal models, Leao's spreading depression has been postulated as the basis for the slowly expanding scintillating scotoma of migraine aura, but has never been directly observed in human cortex. In the present report, two patients with lesions near somatosensory cortex are described who developed episodes of slowly spreading numbness reminiscent of migraine aura. Quantitative comparison was made between these symptoms and experimental models of Leao's spreading depression. The rate of spread, duration, and characteristics of the sensory deficits suggested that cortical spreading depression underlies the pathophysiology of these episodes. Even though their symptoms more resembled those described in migraine than in epilepsy, anticonvulsant medication prevented further episodes in both patients. These two cases provide further, albeit indirect evidence for the existence of spreading depression in human cortex. Clinical criteria are suggested to differentiate the symptoms of migraine aura and epilepsy in the sensory cortex.

Comment: The slow build-up and march of "migrainous" neurological symptoms seems to

differentiate migraine aura from the transient neurological deficits caused by thromboembolic disease. However, a similar "march" may be seen with structural lesions.

(*J Epilepsy* 1998;11(2):110-115)

Initial exploration of pulsing electromagnetic fields for treatment of migraine

Sherman RA, Robson L, Marden LA.

Two studies were conducted during which 23 patients with chronic migraine were exposed to pulsing electromagnetic fields over the inner thigh. In an open study, 11 subjects kept a a-week headache log before and after 2 to 3 weeks of exposure to pulsing electromagnetic fields for 1 hour per day, 5 days per week. The number of headaches per week decreased from 4.03 during the baseline period to 0.43 during the initial 2-week follow-up period and to 0.14 during the extended follow-up which averaged 8.1 months. In a double-blind study, 9 subjects kept a 3-week log of headache activity and were randomly assigned to receive 2 weeks of real or placebo pulsing electromagnetic field exposures as described above. They were subsequently switched to 2 weeks of the other mode, after which they kept a final 3-week log. Three additional subjects in the blind study inadvertently received half-power pulsing electromagnetic field exposures. The 6 subjects exposed to the actual device first showed a change in headache activity from 3.32 per week to 0.58 per week. The 3 subjects exposed to only half the dose showed no change in headache activity. Large controlled studies should be performed to determine whether this intervention is actually effective.

Comment: Pulsing electromagnetic fields over the inner thigh for 1 hour per day reduce headache frequency in this small group of patients with frequent (3-4 per week) "migraine" attacks.

(*Headache* 1998;38(3):208-213)

The long-term tolerability and efficacy of oral zolmitriptan (Zomig, 311C90) in the acute treatment of migraine. An international study

Adelman JU, Baumel B, Cady RK, Baker CC, Couch JR, Dalessio DJ, Diamond S, Elkind AH, Foster CA, Goldstein J, Katz DA, Kirchner JR, Klapper JA, Kudrow DB, Kunkel R, Landy SH, Licht JM, Linder SL, Loder E, Markley HG, Mathew NT, Meyer JS, Nett R, Packard RC, Perse T, Peters KS, Ramadan NM, Rapoport AM, Rosing HS, Sadowsky C, Saper JR, Sharfman MI, Silberstein SD, Singer RP, Smith R, Solomon G, Solomon S, Stark SR, Swanson JW, Taylor FR, Tepper SJ, Tuchman MM, Vijayan N, Walker J, Ward T, Warner JS, Wendt JK, Winner P, Beran P, et al.

This international open-label study evaluated the tolerability and efficacy of zolmitriptan (Zomig(R), 311C90), a selective 5-HT1B/1D receptor agonist, in the long-term treatment of multiple migraine attacks. Patients who had previously participated in placebo-controlled zolmitriptan studies were recruited. A total of 2058 patients treated 31,579 migraine attacks (average 15 per patient), for up to 1 year. Twenty-six percent of attacks treated with a single

zolmitriptan 5-mg dose were associated with at least one adverse event (24% treated with two doses). The most frequent adverse events included asthenia (14% of patients), nausea (12%), somnolence (10%), dizziness (11%), and paresthesia (11%). The rank order of the most common adverse events was not influenced by sex, age, or number of zolmitriptan doses taken and was similar between attacks 1 and 45. The majority of adverse events (59%) occurred within 2 hours of dosing, were of either mild (59%) or moderate (35%) intensity, of 4 hours' duration or less (67%), and required no further action (94%). Following an initial 5-mg dose of zolmitriptan, the 2-hour headache response rate (reduction in headache pain from moderate or severe before treatment to mild or no pain at 2 hours posttreatment) was 81% in patients treating moderate and severe attacks (19,639 of 24,161). Patients were pain-free at 2 hours in 55% of all attacks (16,510 of 29,808). The efficacy of zolmitriptan was not influenced by age, sex, weight, use of prophylactic antimigraine medication, or association of attacks with menstruation. Analysis of the overall population and a subgroup who treated 30 or more migraine attacks showed that zolmitriptan was consistently effective across attacks. Overall, 67% of patients who treated five or more attacks reported zolmitriptan to be effective in 80% to 100% of attacks. Zolmitriptan produced meaningful migraine relief and improvement in normal activity impairment in 73% and 78% of moderate and severe attacks, respectively. Patients treated recurrence of moderate or severe headache with a second zolmitriptan dose in 32% of attacks which responded to the first dose within 2 hours. Where required, a second zolmitriptan 5-mg dose for treatment of recurrence produced a headache response rate of 90% at 2 hours postdose. Thus, zolmitriptan 5 mg (plus an optional second 5-mg dose for treatment of recurrence) is well tolerated and effective in the acute treatment of multiple migraine attacks over periods up to 1 year.

Comment: Impressive numbers and results. Zolmitriptan provided complete relief in 2 hours or less for 55% of 29,808 attacks. Sixty-seven percent (67%) of patients who treated five or more attacks reported zolmitriptan to be effective in 80% to 100% of attacks.

(*Headache* 1998;38(3):173-183)

Transcranial magnetic stimulation confirms hyperexcitability of occipital cortex in migraine

Aurora SK, Ahmad BK, Welch KMA, Bhardhwaj P, Ramadan NM.

Objectives: We hypothesized that the hyperexcitability of occipital cortex neurons may predispose migraine subjects to develop spreading depression, the putative basis of migraine with aura (MwA). To date there is no direct physiologic correlate confirming this in patients. Accordingly, we evaluated the differences in the threshold of occipital cortex excitation between MwA patients and normal controls (C) using transcranial magnetic stimulation (TMS).

Methods: TMS was performed using the Cadwell MES 10 stimulator. A circular coil 9.5 cm in diameter was applied to the occipital scalp (7 cm above the inion). Stimulator intensity was increased in 10% increments until subjects reported visual phenomena or 100% intensity was reached. Stimulation intensity was then fine-tuned to determine the threshold at which phosphenes were just visualized.

Results: Eleven MwA patients, mean age 37 +/-7 years, were compared with 11 C, mean age 37.7 +/-7 years. The difference in the proportion of subjects with phosphene generation between MwA patients and C was significant (MwA patients 100% versus C 27.3%, p = 0.001). The mean threshold level for MwA patients was 44.2 +/-8.6 versus 68.7 +/-3.1 for C. (p = 0.0001). All threshold levels for MwA patients were lower than the lowest threshold for C; the MwA patient with the lowest threshold had an aura after stimulation.

Conclusions: The threshold for excitability of occipital cortex is lower in MwA patients compared with C. This is a direct neurophysiologic correlate for clinical observations that have indicated hyperexcitability of the occipital cortex in migraineurs.

Comment: This is an important study that would be fairly easy to replicate at other centers. The neurologic changes during aura parallel what is seen when the brain is directly stimulated and resemble what might be predicted if ocular dominance columns were serially activated. Previous direct attempts at measuring spreading depression in humans, either using electrophysiologic techniques or laser Doppler flowmetry, were unsuccessful. Observations of a low intracellular magnesium in the occipital cortex of migraine patients have been seen in the clinical phenomenon of the migraine aura. A low intracellular magnesium would render the cortex more easily excitable via glutamate-activated N-methyl D-aspartate-mediated (NMDA-mediated) receptor mechanisms.

(*Neurology* 1998;50(4):1111-1114)

Variable clinical expression of mutations in the P/Q-type calcium channel gene in familial hemiplegic migraine

Terwindt GM, Ophoff RA, Haan J, Vergouwe MN, vanEijk R, Frants RR, Ferrari MD.

Familial hemiplegic migraine (FHM) is an autosomal dominant subtype of migraine with aura, with half of the families being assigned to chromosome 19p13. We identified missense mutations in a brain-specific calcium channel alpha(1A)-subunit (CACNA1A) gene on 19p13 segregating with FHM and truncating mutations in families with episodic ataxia type 2 (EA-2). Expansions of an intragenic CAG repeat have been shown in autosomal dominant cerebellar ataxia (SCA6). Hence, FHM, EA-2, and SCA6 are allelic ion channel disorders. We analyzed the phenotype-genotype relation in three unrelated FHM families with the calcium channel alpha(1A)-subunit gene mutations I1811L (two families) and V714A (one family). We found mutations in all but three patients with FHM (i.e., three phenocopies). In addition, the I1811L mutation occurred in two patients with "nonhemiplegic" migraine and in one subject without migraine. Cerebellar ataxia was found in both families with the I1811L mutation but not in the family with the V714A mutation. We failed to find expansions of the intragenic CAG repeat in FHM patients with cerebellar ataxia. We conclude that the I1811L mutation causes both FHM and cerebellar ataxia independent of the number of CAG repeats. The I1811L mutation may also occur in "normal" migraine patients, supporting the hypothesis that FHM is part of the migraine spectrum.

Comment: Genetically determined susceptibility is the basic neurobiology of migraine. Identification of the gene for familial hemiplegic migraine on chromosome 19p13 announced the beginning of a large effort to unravel the fundamental defect, or defects, that lead to

migraine. Acetazolamide, which can be useful in some paroxysmal ataxias, is also useful in familial hemiplegic migraine.

(*Neurology* 1998;50(4):1105-1111)

Leao's cortical spreading depression and the somatosensory homunculus: A contradiction?

Vanopdenbosch L, Herroelen L.

We present two clinical cases with presumed cortical spreading depression in a pattern which seems inconsistent with the classical drawing of Penfield and Rasmussen's somatosensory homunculus.

(*Headache* 1998;38(4):322-323)

The Internet and migraine: Headache resources for patients and physicians

Genzen JR.

The Internet enables distribution of headache-related resources to patients and physicians in a manner never before possible. While these opportunities for communication and education open many doors to an increased awareness of migraine, there are also dangers in the free flow of non-peer-reviewed information on the Internet. The practicing physician or headache specialist needs to be aware of what headache-related resources are available on the Internet both to recommend information to patients and to know what false information is being spread to headache sufferers. The purpose of this article is twofold: (1) to outline the types of headache-related information available on the Internet, including actual examples that the astute physician can view as time permits, and (2) to present examples of how such information can be biased, inaccurate, and potentially problematic for the curious patient or physician.

(*Headache* 1998;38(4):312-314)

5-HT1B receptor polymorphism and clinical response to sumatriptan

Massen-VanDenBrink A, Vergouwe MN, Ophoff RA, Saxena PR, Ferrari MD, Frants RR.

The 5-HT1 receptor agonist, sumatriptan, is highly effective in the treatment of migraine. Some patients, however, do not respond or experience recurrence of the headache. In addition, some patients report chest symptoms after sumatriptan. We investigated whether these different responses could he attributed to genetic diversity of the 5-HT1B receptor, which most likely mediates the therapeutic action and the coronary side effects of sumatriptan. Allele frequencies of two polymorphisms in the 5-HT1B receptor gene (G861C and T-261G) were

investigated in migraine patients with consistently go27). Allele frequencies (G:0.74; C:0.26 at nt 861 and T:0.39; G:0.61 at nt -261) did not differ between patient groups, indicating that genetic diversity of the 5-HT1B receptor does not seem to be involved In the different clinical responses to sumatriptan.

Comment: There was no evidence that gentic polymorphism of the 5-HT1B receptor was responsible for the variable response to sumatriptan.

(*Headache* 1998;38(4):288-2910

Rizatriptan (MAXALT) for the acute treatment of migraine and migraine recurrence. A placebo-controlled, outpatient study

Teall J, Tuchman M, Cutler N, Gross M, Willoughby E, Smith B, Jiang K, Reines S, Block G.

Rizatriptan is a novel 5-HT1B/1D agonist which is rapidly absorbed after oral administration. The efficacy and tolerability of oral rizatriptan (5 mg and 10 mg) were examined in this multicenter, double-blind, outpatient study of 1473 migraineurs which featured randomized, placebo-controlled treatment of migraine recurrences. On experiencing moderate or severe migraine headaches, patients rated headache severity prior to dosing and at 30-minute intervals for 2 hours after dosing. Onset of effect was seen as early as 30 minutes after dosing with rizatriptan 10 mg. At 2 hours postdose, the percentage of patients with pain relief was significantly higher after rizatriptan 5 mg (62%) or 10 mg (71%) compared with placebo (35%). Complete relief was also significantly higher after rizatriptan 5 mg (33%) and 10 mg (42%) compared with placebo (10%). In patients experiencing headache recurrence after initial benefit, further relief was obtained in 71% with rizatriptan 5 mg (placebo 54%) and in 82% with rizatriptan 10 mg (placebo 44%). Complete relief of recurrent headache was obtained in 36% with rizatriptan 5 mg, 49% with rizatriptan 10 mg, and 15% with placebo ($P < 0.05$). The most common drug-related adverse experiences were dizziness, somnolence, asthenia/fatigue, and nausea (the incidences of which were low and dose related). There was no increase in the incidence of adverse experiences after use of up to three doses of rizatriptan within 24 hours. We conclude that both doses of rizatriptan are effective and well tolerated in the acute treatment of migraine and migraine recurrence, with the 10-mg dose preferred as it is more effective with a faster onset of action.

(*Headache* 1998;38(4):281-287)

Serotonergic, catecholaminergic, and cardiovascular reactions to mental stress in female migraine patients. A controlled study

Stronks DL, Tulen JHM, Verheij R, Boomsma F, Fekkes D, Pepplinkhuizen L, Mantel GWH, Passchier J.

This study aimed at the combined assessment of the serotonergic and sympathetic nervous system reactions of migraine patients before, during, and after the induction of mental stress in order to detect the possible role of these reactions in inducing a migraine attack. The responses

to mental stress of the migraine patients were compared to a group of patients suffering from tension headache and a control group, Activation of the sympathoadrenomedullary system due to mental stress was successfully induced in the migraine patients (n = 23), in the tension headache patients (n = 18), and in the control group (n = 22). The results of this study present evidence of increased cardiovascular activity in migraine patients as compared to nonmigraineurs. However, no evidence was found of a specific serotonergic, sympathoadrenomedullary, or cerebrovascular response of migraine patients to mental stress as compared to nonmigraineurs.

(*Headache* 1998;38(4):270-280)

Practicability and acceptance of subcutaneous self-administration of the selective serotonin agonist sumatriptan

Gobel H, Baar H, Beikufner HD, Bohme K, Beckmann-Reinhold A.

To cater to the special situation of much reduced oral bioavailability which occurs in severe migraine attacks with pronounced nausea and vomiting, sumatriptan can also be used in a subcutaneous form that can be self-administered. The aim of this study was to analyze the practicability and acceptance of a method of self-administration ("Glaxo-Pen") for treatment of severe migraine attacks by subcutaneous injection of sumatriptan. The Glaxo-Pen was compared with the conventional autoinjector for subcutaneous administration of sumatriptan. The multicenter study was conducted under practical conditions by 150 office-based physicians in Germany. Patients who commonly suffered from severe migraine attacks were given a careful explanation of how to use the device ("Glaxo-Pen") for self-administration of subcutaneous sumatriptan and were able to practice using it under guidance. They were given a Glaxo-Pen with two sumatriptan refills to take with them for treating their own migraine attacks. The patients used a headache diary to document administration outside the practice session. A total of 376 patients were included in the study. The major findings were that 80% of the patients rated the Glare-Pen "very easy" or "easy" to use, and only 6.4% rated it "difficult" or "very difficult." Compared with the conventional autoinjector, the Glaxo-Pen was rated "much better" or "better" by 77.9% of patients. Only 8.5% considered the Glaxo-Pen "worse" or "much worse" than the conventional autoinjector. The figures show that the great majority of patients found it easy to use sumatriptan for treating severe migraine attacks by self-administration under practical conditions. Thus, especially for patients who suffer from severe nausea, vomiting, or diarrhea during migraine attacks, this method of delivery is an easily used means of arresting migraine attacks.

(*Headache* 1998;38(4):267-2690

Myogenic cerebrovascular autoregulation in migraine measured by stress transcranial Doppler sonography

Heckmann JG, Hilz MJ, Katalinic A, Marthol H, MuckWeymann M, Neundorfer B.

Background and purpose: Transcranial Doppler sonography (TCD) studies may help to

elucidate the nature and role of vascular abnormalities in migraine. Our aim in this study was to evaluate cerebrovascular autoregulative response in migraine patients with and without aura to blood pressure increase using stress TCD.

Patients and Methods: Using transcranial Doppler ultrasound at rest and during ergometer stress (stress TCD), we studied the changes in mean flow velocities and resistance index (RI) in relation to physical stress in the middle cerebral artery. Fifteen migraine patients without aura, 15 migraine patients with aura, and 15 healthy control subjects were examined. Patients suffered from predominantly unilateral headache and were studied during an attack-free period. The Pourcelot's RI as a measure of cerebrovascular reactivity was calculated by dividing the difference between systolic and diastolic velocity by the systolic velocity.

Results: None of the subgroups showed any difference during ergometer exercise with regard to blood pressure, endtidal CO2, heart rate, or mean flow velocity. In all subgroups, sufficient physical stress was achieved. With respect to RI change, migraine patients without aura and healthy controls did not differ ($p>0.05$). However, the RI change of migraine patients with aura was significantly lower than the RI change of migraine patients without aura or healthy subjects ($p>0.05$). The discrimination analysis showed in addition that RI change (absolute and as a percentage) and mean flow velocity change (as a percentage) could be used as diagnostic variables to detect patients with aura symptoms.

Conclusion: Differences exist in cerebrovascular reactivity in migraine patients with aura that may contribute to the neurologic disturbances in these patients during attack. We propose that there is a disorder of myogenic cerebrovascular autoregulation in migraine patients with aura during headache-free intervals.

Comment: Cerebrovascular reactivity was similar for migraine patients without aura and normal controls but different for migraine with aura.

(*Cephalalgia* 1998;18(3):133-1370

Cognitive processing in migraine: A failure to find facilitation in patients with aura

Palmer JE, Chronicle EP.

Recent interest in cognitive processing in migraine has been based on the assumption that cortical hyperexcitability in migraine with aura may manifest itself in the form of response time advantages in migraine as compared to controls. The study reported here attempted to replicate and extend the findings of Wray and colleagues (Brain 1995;118:25-35). Using identical cognitive tasks, three experiments failed to find differences between migraine with aura patients and controls: furthermore, an additional group of patients without aura were also statistically indistinguishable from controls with respect to response times. Error rates were consistently high across experiments, indicating that subjects were responding at or near chance levels. These findings cast doubt on the utility of straightforward cognitive psychological methods for the study of cortical hyperexcitability in migraine. Some theoretical difficulties concerning the interpretation of response times in the context of migraine pathophysiology are discussed.

Comment: Unlike the study reported by Wray et al. (Brain 1995), this study found no differences between migraine with aura patients and normal controls. Pschological methods may not be the best method for studying cortical hyperexcitabiity in migraine.

(*Cephalalgia* 1998;18(3):125-132)

Multiple-attack efficacy and tolerability of sumatriptan nasal spray in the treatment of migraine

Diamond S, Elkind A, Jackson RT, Ryan R, DeBussey S, Asgharnejad M.

Objective: Sumatriptan hemisulfate nasal spray may provide a useful therapeutic option for patients with migraine who find injectable medications inconvenient or uncomfortable and for patients whose migraine-associated nausea and vomiting preclude the use of oral medication. This study was the first US trial to evaluate the effects of sumatriptan nasal spray administered for multiple migraine attacks.

Design and Interventions: Sumatriptan nasal spray (5, 10, or 20 mg) was administered via a 1-shot nasal applicator into either nostril for up to 3 migraine attacks occurring over 6 months in a randomized, double-blind, parallel-group, placebo-controlled study.

Setting: Fifty-six outpatient clinical centers in the United States.

Patients: A total of 1086 men and women diagnosed with migraine with or without aura per International Headache Society criteria.

Main Outcome Measures: Percentage of patients with headache relief (moderate or severe predose gain reduced to mild or none); percentage of patients with no or mild (vs moderate or severe) clinical disability; percentage of patients with nausea, vomiting, photophobia, or phonophobia; adverse events; clinical laboratory test results.

Results: Across attacks, headache relief in the 20-, 10-, and 5-mg drug and placebo groups was experienced 120 minutes postdose by 60%, 54%, 44%, and 32% of patients, respectively ($P<.05$ for each sumatriptan nasal spray group vs placebo, for the 10-mg vs 5-mg drug group, and for the 20-mg vs 5-mg drug group). Two thirds of the 20-mg patients treating 3 attacks experienced relief at 2 hours postdose for at least 2 of 3 attacks. Clinical disability scores at 120 minutes in the 20-, 10-, and 5-mg drug and placebo groups reflected no or mild impairment in 70%, 67%, 57%, and 50% of patients, respectively ($P<.05$ for the 10-or 20-mg drug group vs placebo group, and for the 20-mg vs 5-mg drug group). Similar efficacy rates were observed for nausea, photophobia, and phonophobia. For all parameters, individual-attack efficacy rates did not differ from across-attack rates. The incidence of adverse events was not dose related. The most frequently reported adverse event in the active treatment groups was taste disturbance (bad, bitter, or unpleasant).

Conclusions: Sumatriptan hemisulfate nasal spray (5, 10, or 20 mg) is effective and well tolerated in the treatment of multiple migraine attacks. The 20-mg dose was associated with the highest efficacy rates across the greatest number of parameters.

(*Arch Fam Med* 1998;7(3):234-240)

Effects of ergotamine on myocardial blood flow in migraineurs without evidence of atherosclerotic coronary artery disease

Gnecchi-Ruscone T, Lorenzoni R, Anderson D, Legg N, Tousoulis D, Winter PDO, Crisp A, Camici PG.

The effects of intravenous ergotamine (0.25 mg) on basal and hyperemic (dipyridamole) myocardial blood flow (MBF), measured with positron emission tomography and (H2O)-O-15, were assessed in 15 migraineurs in a double-blind, randomized, placebo controlled, crossover study. Ergotamine produced a 27% reduction in hyperemic MBF (2.62 +/-0.11 vs 3.72 +/-1.05 ml.min(-1).g(-1); $p < 0.05$), a 31% reduction in the coronary vasodilator reserve (1.81 +/-0.50 vs 2.71 +/-1.15; $p < 0.01$), and a 55% increase in minimal coronary resistance (42.2 +/-15 vs 26.7 +/-8 mm Hg.min.ml(-1)g(-1); $p < 0.001$), suggesting vasoconstriction of the coronary microcirculation.

(*Am J Cardiol* 1998 1;81(9):1165)

Role of anticardiolipin antibodies in young persons with migraine and transient focal neurologic events: A prospective study

Tietjen GE, Day M, Norris L, Aurora S, Halvorsen A, Schultz LR, Levine SR.

Anticardiolipin antibodies (aCL) are a risk factor for cerebral ischemia. In migraine, the association is controversial, with widely varying results in different small series. The controversy in part may be due to the inherent difficulty in distinguishing the transient focal neurologic events (TFNE) of migraine from TIA. To assess the frequency of aCL in migraine, we prospectively evaluated consecutive adults under 60 years of age with migraine without aura and with recent TFNE (<24-hour duration) clinically suggestive of either migraine with aura or TIA. We concomitantly enrolled persons with no CNS disease. Each person was interviewed and had blood drawn for solid-phase ELISA with IgG and IgM aCL isotyping. Neuroradiologic studies were reviewed. Patients with TFNE were followed every 6 months for the duration of the 3-year study. The frequency of aCL positivity (IgG >20, IgG >40, IgM >7.5) for the 645 patients with TFNE (8.8, 3.1, 4.2%), the 518 persons in the TFNE subgroup with migraine with aura (8.9, 3.3, 4.1%), the 497 persons with migraine without aura (7.0, 2.0, 3.6%), and the 366 control subjects (9.3, 3.6, 3.9%) did not differ significantly between groups. In TFNE patients with elevated aCL titer, the association was positive with diabetes mellitus, TFNE duration <15 minutes, and diplopia and was negative with hemiparesis, tinnitus, and family history of stroke. Findings on imaging consistent with cerebral ischemia were more frequent in aCL-positive persons. The short-term risk of stroke was uniformly low. In young persons, aCL is not associated with migraine or with TFNE, although diabetes mellitus, negative family history of stroke, and brief duration of symptoms (including diplopia) may predict immunoreactivity. Imaging studies suggest an ischemic etiology of TFNE in this cohort.

Comment: In an earlier mixed retrospective and prospective study of 68 patients, Tietjen et al. found found that certain clinical features, namely, brief monocular visual loss, hemisensory symptoms, and absence of a family history of migraine, were predictive of a positive cardiolipin antibody (aCL), whereas the incidence of headache, parental migraine, binocular positive visual symptoms, and paresthesias in the negative aPL group paralleled that of migraineurs. Welch earlier recommended "Patients with the diagnosis of migraine with aura should always be screened for the presence of aPL (antiphospholipid antibodies). If there is a history of previous spontaneous abortion, venous or large artery thrombosis, or clinical features to suggest rheumatological disorder, then a full evaluation with VDRL, ANA, aCL, and lupus anticoagulant testing should be carried out (The Headaches, edited by J. Olesen, P. Tfelt-Hansen, and K. M. A. Welch. Raven Press, Ltd., New York (C) 1993)." Stroke specialists see the rare patient with migrainous infarction but screening for coagulopathies and vasculopathies is generally unrewarding for patients with typical visual aura with periodic migraine-like headaches.

(*Neurology* 1998;50(5):1433-1440)

Familial typical migraine: Linkage to chromosome 19p13 and evidence for genetic heterogeneity

Nyholt DR, Lea RA, Goadsby PJ, Brimage PJ, Griffiths LR.

Migraine is a frequent familial disorder that, in common with most multifactorial disorders, has an unknown etiology. The authors identified several families with multiple individuals affected by typical migraine using a single set of diagnostic criteria and studied these families for cosegregation between the disorder and markers on chromosome 19, the location of a mutation that causes a rare form of familial hemiplegic migraine (FHM). One large tested family showed both cosegregation and significant allele sharing for markers situated within or adjacent to the FHM locus. Multipoint GENEHUNTER results indicated significant excess allele sharing across a 12.6-cM region containing the FHM Ca2+ channel gene, CACNL1A4 (maximum nonparametric linkage Z score = 6.64, p = 0.0026), with a maximum parametric lod score of 1.92 obtained for a (CAG)(n) triplet repeat polymorphism situated in exon 47 of this gene. The CAG expansion did not, however, appear to be the cause of migraine in this pedigree. Other tested families showed neither cosegregation nor excess allele sharing to chromosome 19 markers. HOMOG analysis indicated heterogeneity, generating a maximum HLOD score of 3.6. It was concluded that Chr19 mutations either in the CACNL1A4 gene or a closely linked gene are implicated in some pedigrees with familial typical migraine, and that the disorder is genetically heterogeneous.

Comment: If migraine is genetically heterogeneous, could the pathophysiologic mechanism for migraine attacks also be heterogeneous? Syndromic diagnosis does not equal pathophysiologic or etiologic homogeneity. Diagnoses are not diseases.

(*Neurology* 1998;50(5):1428-1432)

The economic burden of migraine to society

Ferrari MD.

The financial burden of migraine on society comprises direct costs, associated with medical care, and indirect costs, caused by absence from work and reduced productivity. Recent studies have revealed that direct costs are generally relatively low in Europe, but are much higher in North America, probably because of increased use of emergency room and specialist consultations for the treatment of migraine. Most individuals who experience migraine headaches take medication (over-the-counter, prescription-only or a combination of both) for their condition; in Europe and North America, most patients who experience migraines have consulted a physician at some time because of their condition. In general, the estimated indirect costs of migraine are substantial and are much higher than estimates of direct costs. On average, work losses related to reduced productivity are higher than those related to work absence. These data demonstrate the importance of the societal impact of migraine and illustrate the need for improved strategies to target migraine treatment.

(*Pharmacoeconomics* 1998;13(6):667-676)

Cardiac effects of sumatriptan: Findings of Holter monitoring and review of the literature

Wober C, Wessely P, Frey B, Marterer A, Zeiler K.

The aim of this study was to elucidate possible electrocardiographic effects of sumatriptan in a selected group of patients with severe headache requiring in-patient treatment. The patients (n=21) were treated with sumatriptan in addition to various other compounds and were asked to record any symptoms following the administration of sumatriptan. In addition, Holter monitoring was performed in all subjects. In agreement with other studies, the adverse events reported by the patients were not related to ECG changes and, vice versa, ECG changes were not accompanied by clinical symptoms. The Holter findings before and after administration of sumatriptan were significantly different in three patients, i.e. recurrent episodes of ST depression and increase in extrasystoles. These changes occurred within a period of 1.45 to 18 hours and were not reproducible when Holter monitoring was repeated without sumatriptan. Even though the findings might be explained by spontaneous variability of Holter monitoring or other factors, this study does not definitely discount the possibility that sumatriptan may cause ST segment changes and increase pre-existing extrasystoles. Controlled studies are required to clarify this issue.

(*Wien Klin Wochenschr* 1998 8;110(9):331-337)

Cost of migraine management: A pharmacoeconomic overview

Rapoport AM, Adelman JU.

Migraine is a chronic, sometimes debilitating, condition that tends to afflict young people who are otherwise healthy and productive, Because diagnostic criteria and effective treatment

modalities have not been well taught to physicians, the condition is often undiagnosed, misdiagnosed, and mismanaged, causing unnecessary pain, hardship to the individual, disability, loss of productivity, and increased expense to the healthcare system. This paper discusses a rational approach to the behavioral and pharmacologic treatment of migraine, highlighting the relative costs of preventive and acute care therapies. Several cases are presented to illustrate how the costs of inefficiently managed migraine therapy can be decreased even by using medications that have a higher per-dose cost, as they decrease the pain and disability and actually lower the total cost of managing the patient with migraine.

(*Am J Manag Care* 1998;4(4):531-545)

Cyclic vomiting and elevation of creatine kinase associated with bitemporal hypoperfusion and EEG abnormalities: a migraine equivalent?

Oki J, Miyamoto A, Takahashi S, Itoh J, Sakata Y, Okuno A.

A 13-year-old mentally retarded boy suffered from repeated vomiting attacks since infancy. Each episode lasted 2 to 10 days, and was precipitated by respiratory infection, exercise or stress. During an attack he became irritated, agitated and amnesic, but did not have headaches or seizures. Associated findings were transient elevation of serum creatine kinase (CK) (331-3381 IU/I), and of plasma ACTH and cortisol. The raised CK level was the result of muscle hypertonicity. Ictal EEGs showed delta activity in the front-temporal areas, and inter-ictal IMP-SPECT revealed hypoperfusion in both temporal regions. Unlike the periodic ACTH-ADH discharge syndrome, neither hypertension nor depression developed. These attacks were diagnosed as a migraine equivalent and were suppressed with phenytoin. From the EEG and SPECT findings, we concluded that the vomiting and behavioural changes were related to the paroxysmal vascular abnormality in the temporal regions, but it was not easy to make the distinction between migraine and focal epilepsy. Before a diagnosis of the periodic ACTH-ADH discharge syndrome is made, the possibility of migraine equivalent should be considered.

Comment: Other than migraine, what other neurological disorders cause cyclic vomiting? Children with cyclic vomiting should be referred to specialists familiar with rare disorders like the periodic ACTH-ADH discharge syndrome, familial dysautonomia, ornithine transcarbamylase deficiency, other urea cycle disorders and mitochondrial cytopathy, adrenoleucodystrophy syndromes and simple partial seizures that may present with cyclic vomiting.

(*Brain Dev* 1998;20(3):186-1890

Clinical experience on headache in children: Analysis of 92 cases

Aysun S, Yetuk M.

We analyzed, retrospectively, 92 patients with headache to determine the changes in the order of frequency of causes with the development of neuroimaging studies and its efficacy in the

investigation of patients with headache. The type of headache was redefined according to the International Headache Society (IHS) diagnostic criteria. Migraine was the most frequent cause of headache and the rest in decreasing order were: tension-type headache, sinusitis, and epilepsy. The percentage of the findings relevant to headache in computed tomographic (CT) scans, magnetic resonance images (MRIs), Waters' projection (radiographs), and electroencephalograms (EEGs) were respectively 4.2%, 33.3%, 16%, and 25%. Neuroimaging studies are not necessary in the routine evaluation of patients with headache unless there is an abnormality in the findings. When it is needed, MRI, which has higher yield, can take the place of CT scanning. The most important point is taking a proper history of headache and making a thorough physical and neurologic examination of the patient.

Comment: Neuroimaging is probably not necessary for periodic headaches with features of typical migraine and no high risk features and a normal neurologic examination. However, a normal "thorough" neurologic examination is not adequate to exclude serious intracranial and pericranial pathology with recent onset of symptoms or atypical features. The neurologic examination performed by many primary care physicians does not include testing of praxis, gnosis, or frontal lobe functions. The neurologic abnormalities associated with compressive lesions may be very subtle and missed with the "traditional" neurologic examination taught to medical students. Many patients do not receive funduscopic examination.

(*J Child Neurol* 1998;13(5):202-210

The development and psychometric properties of the MSQOL: A migraine-specific quality-of-life instrument

McKenna SP, Doward LC, Davey KM.

This paper describes the development and testing of the UK version of the Migraine-Specific Quality-of-Life instrument (MSQOL), a measure designed to assess the quality of life of migraineurs. The work was part of an international research study conducted in eight countries, with the initial development work conducted in the UK and the USA. In the UK, interviews were held with 30 patients with migraine, while in the USA, 25 individual interviews were conducted, along with one focus group with 5 participants. Transcripts were produced of the interviews/group discussion and these were used to determine the questionnaire items, which were then considered by an international translation panel. The panel considered the feasibility of translating the items into other European languages. The instrument was then assessed for reliability and validity. The UK version of the MSQOL was shown to have excellent test-retest reliability (0.93 over 2 weeks) and internal consistency (0.92 and 0.93 on the first and second administrations, respectively). Scores on the measure were also found to be related to a comparator measure of well-being and to perceived severity of migraine and disruption caused to patients by the disease. Findings for the other language versions of the MSQOL supported those from the UK, suggesting that the instrument may well be suitable for inclusion in clinical trials.

(*Clin Drug Invest* 1998;15(5):413-4230

Effects of piroxicam-beta-cyclodextrin in the treatment of spontaneous migraine attacks and reserpine-induced headache: Putative serotoninergic involvement in antinociceptive drug activity

Manna V.

Piroxicam-beta-cyclodextrin (PBCD) is a nonsteroidal anti-inflammatory drug with a central analgesic effect apparently independent of the opioid system. 5-Hydroxytryptamine (5-HT) has long been implicated in the pathophysiology of migraine. 5-HT-depleting drugs, particularly reserpine, a 5-HT reuptake inhibitor, seem to cause "typical headache" in migraineurs. A double-blind controlled trial was performed to determine the effects of PBCD versus placebo in the prevention of migraine without aura; the pain characteristics of reserpine-induced headache in migraineurs; and the effects of PBCD as acute therapy for spontaneous migraine attacks and reserpine-induced headache. PBCD rapidly relieved spontaneous attacks and significantly reduced headache frequency when administered as prophylactic treatment of migraine without aura. In patients suffering from migraine, headache was attenuated by acute and prophylactic PBCD administration. These results appear to confirm the involvement of central serotoninergic pathways in the antinociceptive mechanisms of PBCD.

Comment: Reserpine acts by interfering with 5HT uptake by platelets and releases 5HT from platelet storage granules. Kimball, Friedman and Vallejo (1960) first reported that migraine attacks could be induced in migraineurs by intramuscular injection of reserpine. Since that time several groups of workers have shown, in controlled trials, that the injection of 2.5 mg of reserpine subcutaneously will precipitate migraine attacks in a significant number of migraine sufferers. The authors conclusion, however, that piroxicam-beta-cyclodextrin's ability to treat and prevent spontaneous and reserpine-induced migraine attacks "confirms involvement of central serotoninergic pathways" seems like over interpretation of pharmacologic data.

(*Advan Ther* 1998;15(2):75-84)

Altitude-induced migraine headache secondary to pravastatin: Case report

Ramsey CS, Snyder QC.

A 46-yr-old airline captain with many exposures to altitude chamber, fighter, and airliner flight developed migraine-type headaches after exposure to cabin altitudes above 6,000 feet. He had no prior history of chronic headaches or migraine. Symptoms began within days of starting pravastatin for hypercholesterolemia, but had not occurred during 4 yr of treatment with lovastatin. Headache intensity related directly to increasing pressure altitudes above 6,000 ft for periods of time greater than 45 min. Descent below 5,000 ft cabin altitudes relieved headaches. Exposure to barometric pressure changes has been associated with migraine headache. Vascular headaches are also a prominent feature of acute mountain sickness. Although the HMG-CoA reductase inhibitors are reported to be associated with increased occurrence of headache, the mechanism is poorly understood. Migraine headaches may be triggered in previously asymptomatic individuals by unique combinations of trigger factors. However, there have been no prior reports of migraine headaches triggered by the combined exposure to pravastatin and reduced barometric pressure.

(*Aviat Space Environ Med* 1998;69(6):603-606)

Serotonin inhibits trigeminal nucleus activity evoked by craniovascular stimulation through a 5HT(1B/1D) receptor: A central action in migraine?

Goadsby PJ, Hoskin KL.

The development of serotonin (5HT(1B/1D)) agonists as treatments for the acute attack of migraine has resulted in considerable interest in their mechanism of action and, to some extent, renewed interest in the role of serotonin (5-hydroxytryptamine; 5HT) in the disorder. The initial synthesis of this class of compounds was predicated on the clinical observation that intravenous 5HT terminated acute attacks of migraine. In this study the superior sagittal sinus was isolated in the a-chloralose (60 mg/kg IP and 20 mg/kg IV injection supplementary 2 hourly) anesthetized cat. The sinus was stimulated electrically (120V, 250 mu sec duration, 0.3 Hz), and neurons of the trigeminocervical complex in the dorsal C-2 spinal cord were monitored using electrophysiological methods. After baseline recordings in each animal, 5HT (15 mu g/kg/min) was infused for 5 minutes in the presence of either vehicle (group A) or the 5HT(1B/1D) antagonist GR127935 (100 mu g/kg IV injection; group B). The baseline probability of cell firing after sagittal sinus stimulation was 0.61 +/-0.1 at a latency to the fastest peak of 11.1 +/-0.4 msec. In group A, 5HT infusion alone had a small effect of increasing mean blood pressure (12 +/-3 mm Hg), which in itself did not alter cell firing. In group A, 5HT alone had an inhibitory effect on evoked trigeminal activity, which developed 15 to 20 minutes after commencement of the infusion. The inhibition of cell firing lasted for 20 minutes, after which the activity returned to baseline. In group B, the combination of 5HT and GR127935 had no effect on trigeminal cell firing, although the small hypertensive effect was still present. These data indicate that 5HT inhibits evoked trigeminal nucleus firing via the 5HT(1B/1D) receptor at which GR127935 is an antagonist. It is likely that some part of the effect of 5HT in migraine relates to inhibition of trigeminal nucleus activity, just as it is likely that some part of the effect of the triptans is also mediated at this central site and may be complementary to their nonneuronal actions. Moreover, the data highlight the case for describing this class of headache as neurovascular headaches rather than vascular headaches, to recognize the implicit contribution of the trigeminovascular system to their pathophysiology.

(*Ann Neurol* 1998;43(6):711-718)

Intravenous ketorolac vs intravenous prochlorperazine for the treatment of migraine headaches

Seim MB, March JA, Dunn KA.

Objective: To compare IV ketorolac with IV prochlorperazine as the initial treatment of migraine headaches in the ED.

Methods: A prospective, double-blind comparison study was performed, using a convenience sample of 64 patients suffering from migraine headaches presenting to the ED at a tertiary care university teaching hospital. Patients were randomly assigned to receive either 10 mg of

prochlorperazine IV or 30 mg of ketorolac IV. Patients scored the severity of their headaches using a 10-cm visual analog pain scale. An initial mark was made on the scale at the time of entry into the study and later another mark was made on a new unmarked pain scale 1 hour after medication administration. Changes in pain scores within each treatment group and between groups were analyzed using the Wilcoxon rank sum test.

Results: Prior to treatment, the patients assigned to receive prochlorperazine had a median score of 9.2 cm (mean +/-SD pain score of 8.3 cm +/-2.1 cm), while the patients receiving ketorolac had a median score of 9.0 (mean pain score of 8.4 cm +/-1.7 cm). There was no significant difference between the pain scores of the participants in the 2 groups prior to treatment ($p = 0.80$). One hour after medication administration, the patients in the prochlorperazine group had a median score of 0.5 cm (mean 2.1 +/-3.2 cm), while those patients receiving ketorolac had a median pain score of 3.9 (mean 4.0 +/-3.3 cm). The decrease in pain score was significant for both groups of patients ($p = 0.0001$). The change in pain score for the patients in the prochlorperazine group (median 7.1) was significantly greater than the change in pain score for the patients in the ketorolac group (median 4.0; $p = 0.04$).

Conclusion: Although both drugs were associated with a significant reduction in pain scores, benefit over a placebo agent was not tested. Furthermore, the patients who received prochlorperazine IV for migraine headaches had a statistically significant greater decrease in their pain scores than did those receiving ketorolac IV.

(*Acad Emerg Med* 1998;5(6):573-576)

CLUSTER HEADACHE

Acute treatment of episodic and chronic cluster headache with subcutaneous sumatriptan. Results of a 1-year long-term study

Gobel H, Lindner V, Pfaffenrath V, Ribbat M, Heinze A, Stolze H.

The aim of this open prospective study was to investigate the efficacy, safety and tolerability of subcutaneous sumatriptan in the acute treatment of cluster headache. Self-treatment with 6 mg sumatriptan subcutaneously was monitored over a period up to 1 year. Headache parameters were documented by the patients with a headache diary. A total of 2031 attacks in 52 patients were investigated. Treatment with sumatriptan was effective in 88% of the attacks and 57% of the patients were pain-free within 15 min after injection; 42% of the patients became pain-free within 15 min after at least 90% of their attacks. During long-time treatment the efficacy remained unchanged. Of the patients 10% withdrew from the study due to lack of efficacy or adverse events. In total, 62% of the patients reported adverse events,which were serious in 3.8% of the cases. Subcutaneous self-treatment of cluster headache is both highly effective and well tolerated.

(*Nervenarzt* 1998;69(4):320-329)

Craniometric measures in cluster headache patients

Afra J, Cecchini AP, Schoenen J.

Blockade of venous drainage in the cavernous sinus, which may play a pivotal role in the pathophysiology of cluster headache (CH), could be triggered by local inflammation. It could also be favored by a constitutional narrowness of the cavernous sinus region. Before exploring the latter with magnetic resonance imaging (MRI), we determined whether external morphometric skull measures are different among CH patients (n=25), healthy volunteers (n=21), and migraine patients (n=20). All subjects were males of comparable age distribution. Six measures were taken: inion-nasion perimeter, inion-nasion distance over the vertex; distance between the upper ends of tragus; diameter at the level of the temporal fossa; diameter at mid inion-nasion perimeter at ear level; and inion-nasion diameter. CH patients had significantly smaller values than healthy subjects and/or migraine patients in all but one measure (ANOVA and Duncan's post-hoc analysis). This may suggest that they have a narrower anterior/middle cranial fossa, and possibly a narrower cavernous sinus loggia, which needs to be confirmed by a quantitative MRI study.

(*Cephalalgia* 1998;18(3):143-145)

Episodic cluster headache in a community: Clinical features and treatment

Riess CM, Becker WJ, Robertson M.

Objective: To study the clinical features and treatment given to episodic cluster headache patients in the Calgary region.

Patients: Fifty-one (51) patients who responded to a media campaign, had previously been diagnosed by their family physicians, and who met International Headache Society (IHS) criteria for episodic cluster headache, formed the population for this study.

Methods: The media campaign consisted of newspaper advertisements and radio publicity including physician interviews and talk shows. Patients were required to complete a 200-item questionnaire detailing clinical features and treatment of their cluster headache syndrome. Each patient was also interviewed by our research nurse for clarification and proper completion of questionnaire.

Results: Fifty-one percent (51%) of our patients had short headache attacks lasting one hour or less. Almost one-half (45%) had three or four attacks per 24 hour period. Eighty-six percent (86%) had been referred to a neurologist. Sixty-nine percent (69%) had never used oxygen, but of those who had, one-half were still using it. Subcutaneous dihydroergotamine had been tried by 8%. For prophylaxis, 41% had tried methysergide, 31% prednisone, and 4% verapamil. Many patients had been prescribed migraine prophylactic drugs which are ineffective for cluster headache, and some had also undergone dental procedures or nasal and sinus surgeries.

Conclusions: Many cluster headache patients had not, to their knowledge, been prescribed or used the best symptomatic and prophylactic treatments for cluster headache. This should be

addressed through educational programs and through making up-to-date information on the treatment of cluster headache readily available to physicians and patients.

(*Can J Neurol Sci* 1998;25(2):141-145)

Gender ratio of cluster headache over the years: a possible role of changes in lifestyle

Manzoni GC.

Changes in the male-to-female (M/F) ratio of cluster headache (CH) over the years were investigated through a comparative analysis of the distribution of the disease by sex and decade of onset in 482 patients (374M and 108F). Variations over the last few decades were also investigated in the employment rate, level of school education, smoking habit, and coffee and alcohol intake of the population living in the same area as the CH patients. The M/F ratio has fallen from 6.2:1 for patients with CH onset before 1960, to 5.6:1, 4.3:1, 3.0:1, and 2.1:1 for patients with CH onset in the 1960s, 1970s, 1980s, and 1990s, respectively. Correspondingly, in those same decades, the M/F ratio has fallen from 2.6:1 to 2.4:1, 2.2:1, 2.0:1, and 1.7:1, respectively, for the employment rate, and from 8.6:1 to 7.8:1, 3.3:1, 2.5:1, and 1.9:1 for the smoking habit. Such a close correlation suggests that the significant changes that have occurred over the last few decades in the lifestyle of both sexes-and particularly that of women-may have played a major role in altering the gender ratio of CH.
Comment: This article prompted me to look at the male:female ratio of my patients with cluster headache. In the past year I have seen 69 males and 1 female with cluster headache. I'm not so sure the M/F ratio is decreasing as dramatically as this paper suggests.

(*Cephalalgia* 1998;18(3):138-142)

TENSION-TYPE HEADACHE AND OTHER PRIMARY HEADACHES

Time required for improvement of an analgesic rebound headache

Warner JS.

There is typically delayed improvement in analgesic rebound headache after the offending agents have been discontinued. This case history documents that, at times, it might be necessary to omit medications for 6 months until the almost daily headaches cease.

Comment: I see few patients who would be willing to wait six months for an intervention to provide benefit. Discontinuation of analgesics is not a single intervention. There are cognitive and behavioral aspects to the pharmacologic intervention (discontinuation of analgesics). Patients have to trust their physicians sufficiently to accept the idea that discontinuation of analgesics will ultimately be beneficial. Most patients will give it a try for a few weeks with information and education and support. In addition to spontaneous remission and regression toward the mean, these behavioral factors may play a role, especially when improvement is delayed for months. It would be interesting to see if there is a difference between patients

allowed to take a placebo analgesic versus patients required to stop all "as needed" distress-relieving agents.

(*Headache* 1998;38(3):229-230)

Social environment and headache in 8-to 9-year-old children: A follow-up study

Metsahonkala L, Sillanpaa M, Tuominen J.

We studied the occurrence of migraine and nonmigrainous headache and the factors associated with headache in a group of 3580 children. These children belong to a 1-year age cohort which has been followed since birth. When the children were 8 to 9 years old, data on their headaches were gathered through a postal questionnaire. Ninety-five of the children (2.7%) had migraine and 977 (27.3%) reported nonmigrainous headache at the age of 8 to 9 years. Thirty-four percent of the children with migraine had already had headache at the age of 5 years. Children with migraine and children with nonmigrainous headache both reported more often being bullied in school, stress in school, and problems in getting along with other children than children without headache. The association of stress in school with headache was strongest in girls with migraine, even though they reported the least difficulties in school subjects. As many as one third of the boys with migraine reported that they had problems with peer relationships.

(*Headache* 1998;38(3):222-228)

Chronic paroxysmal hemicrania and hemicrania continua: Lack of efficacy of sumatriptan

Antonaci F, Pareja JA, Caminero AB, Sjaastad O.

Attacks of chronic paroxysmal hemicrania are prevented by the continuous administration of indomethacin. Sumatriptan, an agonist of 5-HT1-like receptors, has proven effective in the treatment of cluster headache attacks. There are clear clinical similarities between chronic paroxysmal hemicrania and cluster headache. A natural consequence of these considerations would be to establish whether chronic paroxysmal hemicrania also responds similarly to sumatriptan. Since hemicrania continua is another unilateral headache responsive to indomethacin, it would be meaningful to also include hemicrania continua in such a study. Sumatriptan, 6 mg subcutaneous, was tried in an open fashion in 7 patients (6 women and 1 man) with chronic paroxysmal hemicrania and 7 patients (5 women and 2 men) with hemicrania continua. In chronic paroxysmal hemicrania, the mean interval between the last three attacks prior to sumatriptan treatment (40 +/-23 minutes) was not statistically different from the mean interval between the three attacks subsequent to sumatriptan treatment of an attack (32 +/-20 minutes). In none of the patients did the mean duration of the "test attack" decrease as compared to the attacks antedating the test attack (25 +/-11 minutes and 19 +/-9 minutes, respectively) ($P = 0.027$, Wilcoxon). In 2 patients with chronic paroxysmal hemicrania, placebo (saline) administration did not lead to any change in the interval between attacks. There was a mild, but statistically significant reduction in visual analog scale values for headache intensity in hemicrania continua ($P = 0.04$, Wilcoxon). There was no clear, ie,

clinically meaningful, reduction in visual analog scale values in any particular patient with hemicrania continua. Taken together, these results seem to show that sumatriptan is of no benefit in chronic paroxysmal hemicrania, but may have a partial efficacy in hemicrania continua. However, the latter effect is clinically unimportant. This minor difference in regard to the clinical effect may, nevertheless, be of some interest pathogenetically, indicating minor differences between the two headaches. The lack of sumatriptan effect in chronic paroxysmal hemicrania clearly and markedly strengthens the nonalignment concept in regard to chronic paroxysmal hemicrania and cluster headache.

Comment: Chronic paroxysmal hemicrania and cluster headache have similar symptoms but a different temporal profile and response to therapy. Chronic paroxysmal hemicrania is probably not a "variant" of cluster headache but a different disorder altogether.

(*Headache* 1998;38(3):197-200)

Presentation of chronic daily headache: A clinical study

Spierings ELH, Schroevers M, Honkoop PC, Sorbi M.

We studied the presentation of chronic daily headache in 258 patients from a private headache practice, 50 men and 208 women. Chronic daily headache was defined as headaches, occurring at least 5 days per week for at least 1 year. Seventy-seven percent of the patients experienced the onset of headache before the age of 30. The daily headaches were present on awakening in the morning or came about in the course of the morning in 79% of the patients. In 53%, they were worst in the afternoon or evening. The headaches awoke the patients at night at least once per week in 36%. At least twice per week, they were associated with nausea in 35% of the patients and with vomiting in 9%. Common aggravating factors included light, physical activity, bending over, noise, stress or tension, and menstruation. Ninety-four percent of the patients experienced severe headaches in addition to the daily headaches. In 63%, the severe headaches occurred 10 days per month or less. The daily caffeine intake of the patients averaged 170 mg, and the daily analgesic intake, 1860 mg of aspirin equivalents.

Comment: Chronic daily headache is a nonspecific symptom that can be due to different primary headache syndromes and a variety of etiologies.

(*Headache* 1998;38(3):191-196)

Psychological well-being in older adults suffering from chronic headache

Jelicic M, Kempen GIJM, Passchier J.

Objective: The aim of this study was to examine two components of psychological well-being -life satisfaction and affective well-being -in community-dwelling elderly with (n = 321) and without chronic headache (n = 4955).

Methods: A checklist of chronic medical conditions was used to determine whether

respondents were suffering from headache. Cantril's ladder was employed to measure life satisfaction. The subscale, Mental Health, from the MOS SF-20 was used to assess affective well-being.

Results: Headache sufferers reported lower life satisfaction as well as lower affective well-being. However, the difference in life satisfaction between the two groups disappeared after controlling for comorbidity. The difference in affective well-being disappeared after controlling for neuroticism.

Conclusions: Lower life satisfaction in patients with chronic headache is caused by more comorbid diseases in the headache group. Lower affective well-being in headache sufferers is due to higher levels of neuroticism in the headache group.

(*Headache* 1998;38(4):292-294)

The hypnic headache syndrome: report of three new cases

Morales-Asin F, Mauri JA, Iniguez C, Espada F, Mostacero E.

Three new cases compatible with hypnic headache syndrome (HHS) are presented. The patients were 70, 77, and 79 years of age (2F, 1M). They described a history of nocturnal headache ranging from 5 months to 7 years. One patient was afflicted with diffuse pain but the other two had unilateral pain. In one patient headache was clearly related with dreams, but in the other two this point could not be confirmed. Except for headache being unilateral in two cases, the remaining HHS criteria were present. It is noteworthy that pain responded to flunarizine in two patients.

(*Cephalalgia* 1998;18(3):157-158)

A review of the treatment of primary headaches. Part II: Tension-type headache

Damico D, Grazzi L, Leone M, Moschiano F, Bussone G.

This paper reviews pharmacological and other approaches currently used to treat tension-type headache (TTH), and examines aspects of the classification and pathogenesis of this common complaint. Accurate diagnosis is essential before treatment is prescribed and should involve complete history taking, thorough neurological examination and evaluation of possible associated factors. The most frequently used drugs for the acute treatment of TTH are non-steroidal anti-inflammatory drugs (NSAIDs) of which only some have been shown to be efficacious in placebo-controlled trials. Amitriptyline remains the first choice treatment for prophylaxis. Other antidepressants, muscle relaxants and benzodiazepines may be used, but few have been evaluated adequately in placebo-controlled trials. Biofeedback and relaxation training, demonstrated efficacious by controlled studies, may be used when the aim is to avoid the side effects of pharmacological treatment.

(*Ital J Neurol Sci* 1998;19(1):2-9)

Epidemiologic and clinical characteristics of migraine and tension-type headache in Korea

Roh JK, Kim JS, Ahn YO.

This is the first population-based epidemiologic study of chronic headache in South Korea. The diagnosis and classification of headache was according to the criteria of the International Headache Society. Sixty-eight percent of the studied population experienced headache during the preceding year. The estimated prevalences were 22.3% for migraine (male 20.2%, female 24.3%) and 16.2% for tension-type headache (male 17.8%, female 14.7%). In migraine, the 15-to 18-year age group showed maximal prevalence in both sexes (male 28.5%, female 34.7%). The prevalence of tension-type headache was highest in the 50-to 59-year age group in men (24.2%) and in the 20-to 29-year age group in women (20.2%). In migraine, headache intensity was more severe in women than in men, but in tension-type headache there was no difference in the severity of headache between the sexes. Phonophobia was the most common associated symptom of migraine (65.1%). In the migraine with aura group, the most common aura was visual disturbance, including scintillation and image distortion (82.3%). Only 24.4% of migraineurs and 12.3% of patients with tension-type headache had ever consulted a doctor for headache. The prevalence of migraine was not lower than in western countries and much higher than in previous studies conducted in other Asian countries.

(*Headache* 1998;38(5):356-365)

The hypnic ("alarm clock") headache syndrome

Dodick DW, Mosek AC, Campbell JK.

Hypnic headache syndrome is a rare, sleep-related, benign headache disorder. We report 19 new cases (84% females) with follow-up data. The mean age at headache onset was 60.5 +/-9 years (range 40-73 years). Headache awakened the patients from the night's sleep at a consistent time, usually between 1:00 and 3:00 a.m. (63%); three patients (16%) reported that identical headaches could occur also during daytime naps. Headache frequency was high, occurring more than 4 nights/week in 68% of the patients. Headache resolution occurred within 2 h in 68% of patients. Neurologic examination, laboratory studies, and brain imaging were unrevealing at the time of diagnosis. Headache severity largely remains unchanged or attenuates over time, but frequency may vary in either direction. Only one patient had spontaneous relief from headache. Four patients (24%) achieved permanent suppression of headache with medication, and two were able to abort individual headache attacks. Caffeine in a tablet or beverage was helpful in four patients. Lithium carbonate therapy caused side effects requiring cessation of treatment in four patients.

(*Cephalalgia* 1998;18(3):152-156)

SUNCT syndrome. Two cases in Argentina

Raimondi E, Gardella L.

Two patients suffering from SUNCT syndrome are presented. Some features are remarkable. The first patient was a 69-year-old man whose first crisis was located in the right supraorbital region. After a 4-month spontaneous remission, the pain returned to the upper part of the cheek, radiating to the supraciliary region on the same side, with lacrimation and conjunctival injection. Rhinorrhea was absent. The painful attacks were triggered by head movements. Clinical improvement occurred with carbamazepine treatment. The second patient was a 48-year-old woman whose painful attacks lasted from 30 to 45 seconds followed by a burning sensation lasting 2 hours. Autonomic signs such as conjunctival injection, lacrimation, and edema and ipsilateral ptosis of the upper lid were rather marked. There was never any rhinorrhea. Her attacks were triggered by head and eye movements. She responded to the administration of corticosteroids and carbamazepine. According to these features, the two patients had SUNCT syndrome, and the positive carbamazepine response suggests a relationship with trigeminal neuralgia.
Comments: Patients with SUNCT syndrome typically complain of unilateral headache with frequent (5 to 30 times per hour), short-lasting (15 to 60 seconds) attacks of pain. The pain occurs in and around one eye and is accompanied by ipsilateral conjunctival injection, lacrimation, and forehead sweating.

(*Headache* 1998;38(5):369-371)

Relationships between arousal-related moods and episodic tension-type headache: A biopsychological study

Cathcart S, Pritchard D.

An exploratory study was conducted examining arousal-related moods and episodic tension-type headache. Twelve subjects meeting International Headache Society criteria for episodic tension-type headache and 12 headache-free controls recorded headache activity and mood eight times daily for 14 consecutive days. Moods were measured using the Activation-Deactivation Adjective Check List, a self-report list that subjectively represents general arousal along two dimensions of Tension and Energy. Headache subjects had higher Tension levels than controls even in the absence of pain, and greater variation in this dimension as well. Within the headache group, Tension during pain-free periods was significantly lower than when experiencing headache, and was correlated with headache activity. The results were taken to support Thayer's (1989) biopsychological model of mood and arousal, and are discussed in terms of the model's heuristic value for general arousal and headache research.

(*Headache* 1998;38(3):214-221)

The treatment of tension-type headache. Guidelines of the German Migraine-and Headache Society

Pfaffenrath V, Brune K, Diener HC, Gerber WD, Gobel H.

Tension-type headache is characterised by a dull-pressing and bilateral headache in which the autonomic symptoms typical of migraine are absent or only weakly present. The IHS-Classification differentiates between an episodic (< 180 days/year) and a chronic (> 180 days/year) tension-type headache. The prevalence of chronic tension-type headache is 3%. There are no particular pathological findings characteristic for this disease. The differential diagnosis of tension-type headache includes cervicogenic headache and analgesic induced headache. A combination headache is defined by a daily tension-type headache superimposed with migraine attacks. According to modern pathophysiological concepts central changes in descending pain control systems interact with peripheral disturbances such as a raised myofascial pain sensitivity. Simple analgesics like acetylsalicylic acid and paracetamol, or ibuprofen and naproxen as substitutes can be given occasionally or for short episodes of tension-type headache. For the long-term drug prophylaxis amitriptyline is the first choice. Doxepine, clomipramine, mianserin, maprotiline and the anticonvulsant valproate may also be used as alternatives. The duration of treatment is at least six months. Additionally, or as an alternative behavioural medical procedures like stress training, relaxation techniques and biofeedback can be used. Acupuncture, accupressure and transcutaneous nerve stimulation as well as physiotherapy or chiropractic procedures are of no proven benefit.

(*Nervenheilkunde* 1998;17(2):91-100)

Melatonin-responsive headache in delayed sleep phase syndrome: Preliminary observations

Nagtegaal JE, Smits MG, Swart ACW, Kerkhof GA, vanderMeer YG.

The occurrence of headache and its change after treatment with melatonin 5 mg were studied in 30 patients with delayed sleep phase syndrome. The medication was taken 5 hours before the endogenous nocturnal plasma melatonin concentration had reached 10 pg/mL. Three women (aged 14, 14, and 23 years) suffered from chronic tension-type headache. Their headache disappeared within 2 weeks after the start of treatment with melatonin. One 54-year-old man suffered from disabling migraine attacks without aura, twice a week. After starting melatonin treatment, only three migraine attacks were reported in 12 months. Ever since his 40s, a 60-year-old man complained of cluster headache episodes lasting about 2 months, twice a year. In the year since starting melatonin treatment, only one 5-day cluster episode occurred. Nocturnal melatonin secretion in the patients with delayed sleep phase syndrome and headache did not differ significantly from that in the patients with the sleep disorder but without headache. Melatonin may be helpful in patients with headache who are suffering from delayed sleep phase syndrome. Its effectiveness may be due to modification of vascular and nociceptive systems or to its chronobiological action which adjusts the patient's biological clock to his/her life-style.

Comment: Patients with delayed sleep phase syndrome usually complain of difficulty getting up on time in the morning for school or work, of extreme difficulty initiating sleep, or both. Symptoms most often begin during adolescence: frustrated parents may bring the problem to medical attention because of their inability to get their deep-sleeping teenager out of bed in time for school. Patients who have not completely abandoned arising at conventional times on

weekdays show foreshortened sleep (2 to 5 hours) on such days and lengthy (9 to 18 hours) sleep durations with late morning to mid-afternoon arising times on weekends. Delayed sleep phase syndrome patients usually maintain sleep without interruption, but sleep on a clearly delayed schedule. The original and still the most efficient treatment for delayed sleep phase syndrome, known as chronotherapy, consists of progressive, daily, 3-hour delays of bedtime and arising time until the patient's sleep schedule matches the desired social schedule

(*Headache* 1998;38(4):303-307)

The platelet serotonin transporter in primary headaches

Bendtsen L, Mellerup ET.

Serotonin (5-HT) plays a major role in the pathophysiology of primary headaches. The presynaptic 5-HT uptake mechanism, which is important for the regulation of 5-HT levels in the neuronal synapses, can be examined indirectly by measuring the number of 5-HT transporters in membranes from platelets. The aim of the present study was to investigate the platelet 5-HT transport system in patients with primary headache disorders. B-max, an index of the number of platelet 5-HT transporters, was measured in 40 patients with chronic tension-type headache, in 30 patients with migraine without aura, and in 40 healthy controls using a binding analysis with tritiated paroxetine as the ligand. The B-max was 664 (589-846) (median (quartiles)) fmol/mg protein in patients with tension-type headache and 662 (534-781) fmol/mg protein in healthy controls, P = 0.40. The B-max was 675 (558-747) fmol/mg protein in patients with migraine, which was not significantly different from the B-max in controls, P = 0.94. In conclusion the present results indicate that the number of platelet 5-HT transporters is normal in patients with chronic tension-type headache and in patients with migraine without aura.

Comment: The cell bodies of serotonergic neurons are located in the raphe nuclei and superior central nucleus, and their axons project widely throughout the CNS-to the entire neocortex, rhinal cortex, thalamus, hypothalamus, limbic structures, reticular formation, locus ceruleus, cerebellum, and spinal cord. Do changes in serotonin metabolism in platelets reflect CNS changes? Biological psychiatrists have been interested in serotonin metabolism for affective disorders for many years. Decreased serotonin uptake into platelets has been observed in patients with depressive disorders. H3-imipramine binds to serotonin uptake sites in platelets as well as brain, and a highly significant decrease in the number of H3-imipramine-binding sites with no significant change in the apparent affinity constant has been observed in platelets from depressed patients compared with those from control subjects. While it has been proposed that the decreased platelet H3-imipramine binding observed in depressed patients may reflect a deficiency in the platelet serotonin transport mechanism in those patients, recent studies employing H3-paroxetine cast some doubt on this proposal. Paroxetine is a more specific ligand than imipramine for labelling the serotonin transporter protein. And in several recent studies, there was no difference in the binding of H3-paroxetine in platelets when values in depressed patients and control subjects were compared.

(*Eur J Neurology* 1998;5(3):277-282)

Medication patterns of recurrent headache sufferers: a community study

Forward SP, McGrath PJ, MacKinnon D, Brown TL, Swann J, Currie EL.

This community-based telephone survey determined medication patterns of 274 frequent headache sufferers who reported 12 or more headaches a year. Headaches were classified using the International Headache Society's (IHS) criteria. Participants reported on 465 types of headaches: 129 tension headaches, 158 migraine headaches, 8 chronic tension headaches, and 148 headaches which were unclassifiable using IHS criteria. Females (n=133) reported an average of 1.9 types of headache and males (n=141) reported 1.5 headache types. Fifty-six percent of respondents used acetaminophen for tension-type and 60% used acetaminophen for migraine. One percent used prescription medication for tension headache and 12% used prescriptions for migraine. The perceived effectiveness of over-the-counter medication was approximately 7 on a scale of 0-10 for tension headaches and 6 for migraine. Both tension-headache and migraine-headache sufferers waited about 1 h before taking any medication. Tension-headache sufferers waited until the headache was above 5 on a 0 to 10 scale (4.6 for migraine). It is possible that more aggressive use of medication might improve headache management.

(*Cephalalgia* 1998;18(3):146-151)

In-patient treatment of chronic daily headache using dihydroergotamine: a long-term follow-up study

Pringsheim T, Howse D.

Background: The treatment of chronic daily headache (CDH) due to medication overuse remains a common and difficult problem. For selected patients refractory to outpatient management we have used a treatment protocol using dihydroergotamine (DHE) as introduced by Raskin, during a brief (typically 48 hours) in-patient stay. While many studies have documented the short-term efficacy of the DHE protocol, there are limited data on its long-term effects. The purpose of this study was to evaluate the efficacy of the protocol on headache frequency and severity, analgesic use, absences from work, and quality of life, at three months post treatment and the present time.

Methods: A retrospective chart review of all patients admitted for the DHE protocol from 1991 to 1996 revealed 174 cases. Of these, 132 patients were interviewed by phone.

Results: The DHE protocol was shown to decrease headache frequency, severity, headache medication use, and absences from work both at three months and the time of interview.

Conclusion: This study has the largest patient base and the longest follow-up period for the use of DHE for CDH. The results confirm that the DHE protocol is helpful in breaking the cycle of CDH, although the long-term outcomes of this study are more conservative than ether studies have reported.

(*Can J Neurol Sci* 1998;25(2):146-150)

Twelve cases of analgesic headache

Symon DNK.

Analgesic headache occurs when drugs given for the treatment of headache aggravate symptoms. The condition is well recognized in adults but has not been described before in children in whom it may be induced by mild analgesics such as paracetamol used alone. Twelve children (nine girls and three boys, aged 6 to 16.5 years) with analgesic headache (from three months to 10 years) are reported. Five children were taking paracetamol alone, six were taking paracetamol with codeine, and one child was taking ibuprofen. The abrupt withdrawal of analgesic drugs was successful in eight of the children; two had episodic migraine headaches; one had headaches but with reduced frequency; and one returned to analgesic abuse.

(*Arch Dis Child* 1998;78(6):555-556)

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Abstract Volume 12 Issue 6 (1998) pp 383-388

übersichten: 2-Arylpropionsäuren Stellenwert in der Schmerztherapie 2-Arylpropionic acids. Role in pain therapy

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Zusammenfassung

Für über 100 Jahre waren Azetylsalizylsäure, Phenazon und seine Derivate sowie Paracetamol die bevorzugten Analgetika für die Behandlung passagerer Schmerzen im Gefolge von Infektionen, Verletzungen und kleineren chirurgischen Eingriffen, aber auch gegen Spannungskopfschmerzen und muskuloskelettale Beschwerden. Innerhalb der vergangenen Jahrzehnte sind diese Wirkstoffe z. T. durch 2-Arylpropionsäure-Derivate abgelöst und ergänzt worden. Einige Prototypen dieser Substanzgruppe wie Ibuprofen, Ketoprofen und Naproxen haben in einigen Ländern sogar den Status der Rezeptfreiheit erreicht - offensichtlich aufgrund eines günstigen Wirkungs- und Nebenwirkungsprofils. Innerhalb dieser Gruppe von Wirkstoffen bestehen allerdings erhebliche pharmakodynamische und pharmakokinetische sowie geringe

toxikologische Unterschiede, die sie für die Therapie von passageren Schmerzen als unterschiedlich geeignet erscheinen lassen.

Abstract

The antipyretic analgesics still comprise the most widely used group of analgesic compounds. Until twenty years ago, aspirin, phenazone derivatives and acetaminophen had been used as standard remedies for intercurrent harmless pain conditions in connection with infections, trauma, small surgeries, but also for **tension headache** and other painful conditions. During the last decades, this group has been supplemented by a variety of 2-arylpropionic acids being primarily developed for the treatment of rheumatic pain and inflammation. Some of them (e.g. **ibuprofen**, ketoprofen and naproxen) have been given over-the-counter status in some countries because of their relative safety at low doses. Nevertheless, pharmacodynamic and pharmacokinetic differences among the various substances of this group make them suitable to a different degree for the treatment of pain conditions.

Schlüsselwörter Antipyretische Analgetika · 2-Arylpropionsäuren · Enantiomere · Schmerz

Key words Antipyretic analgesics · 2-arylpropionic acids · Enantiomers · Pain

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Mirtazepine: heir apparent to amitriptyline?

Davis MP, Dickerson ED, Pappagallo M, Benedetti C, Grauer PA, Lycan J.

Harry R. Horvitz Center for Palliative Medicine, Cleveland Clinic Taussig Cancer Center, Cleveland, Ohio, USA.

"What's new in therapeutics?" will examine and evaluate drugs that may have a place in hospice, palliative, and long-term care. Mirtazepine will be examined and evaluated. Mirtazepine is a potential alternative anti-depressant with multiple additional benefits. It is an atypical anti-depressant, which has both noradrenergic and specific serotonergic receptor antagonism (NaSSa), and a unique pharmacological profile. Mirtazepine appears to be a "designer drug" for palliative medicine with a number of benefits, but cost may be a drawback.

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